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OF OUR WORLD-WIDE KNOWLEDGE OF NUTRITION

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ON SOME ASPECTS OF PROTEIN NUTRITION*

By PAUL GYÖRGY, M.D.†

PROTEIN as a nutrient and participant in metabolic reactions is at present in the foreground of medical-scientific interest.

Protein deficiency, or more specifically protein malnutrition, is a world-wide problem, involving chiefly the large tropical belt of the world, stretching from Indo-China over Burma, Indonesia, India, Ceylon, the Near East, and almost all of Africa, to the West Indies, Central and parts of South America. In its classical form, protein malnutrition in these tropical countries is seen predominantly in infants in the post-weaning period up to 6–7 years. It is clinically very similar, if not identical to, the condition known as "Mehlnährschaden" or "starchy food dystrophy" and seen in children fed a diet low in protein and high in cereals. In some parts of Italy, from the end of the last war through the present years, this starchy food dystrophy assumed great proportions and became an important public health problem. Both this old European and the tropical form of protein malnutrition are characterized by generalized edema, chronic bulky diarrhea with remnants of undigested food in the feces, hypoproteinemia, and atrophy of small intestinal mucosa and of the pancreatic acini, as well as by fatty infiltration of the enlarged liver. Additional characteristics of the tropical entity are pigmentation, ulceration of the skin, and depigmentation of the hair, which in Negroes becomes reddish, straight, and coarse. Similar depigmentation of the hair with reddish discoloration may also be observed in American Indian children suffering from protein malnutrition, as was seen by us in Guatemala.

The cutaneous manifestations are not limited to the parts of the body exposed to sunshine, such as hands, feet, head, and neck, as in pellagra, but are seen chiefly over the buttocks and thighs. Mental apathy and often peevishness are outstanding psychological attributes of children with severe protein malnutrition.

For this tropical variety of protein malnutrition, the name "kwashiorkor" has lately come into general use. It has been claimed that in British West African language the word kwashiorkor indicates "red boy," from the corresponding change in the color of the hair in these malnourished children.

At the Nutritional Conference held under the auspices of the World Health Organization (WHO) and the Food and Agricultural Organization of the United Nations (FAO) in December, 1952, in the Gambia, British West Africa, protein malutrition, together with its clinical manifestation, kwashiorkor, was the chief topic of discussion. Workers in the field maintained that in kwashiorkor, as in starchy food dystrophy, the total daily caloric intake was, as a rule, not dangerously reduced; instead, only the proportional protein supply fell below the necessary minimum both in

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* Mellon Lecture, held on November 20, 1953 before the Society for Biological Research, University of Pittsburgh.

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quality and quantity. Mathematically, this may be expressed as follows: If the relative proportion of calories supplied by protein reaches a level of 15 to 20 per cent of total calories in the daily diet, the protein requirement is sufficiently covered. This figure is reached in cow's milk where, as a matter of fact, the ratio of protein calories to total calories exceeds 20 per cent. When the percent of total calories supplied by protein is from 10 to 15 per cent (especially if the protein is of vegetable origin) the resistance of the organism is lowered. This is seen especially in cases of chronic infection, such as malaria, tuberculosis, and massive intestinal infestation. These infections may be followed by manifestations of at least mild kwashiorkor. A ratio below 10 per cent represents definite danger, usually with clinical manifestations of protein malnutrition, including signs and symptoms of kwashiorkor.

The only obvious exception to this rule is human milk, in which the ratio of calories supplied by protein to total calories is only 6 to 7 per cent. Since this ratio falls below the 10 per cent minimum, it should, in itself, indicate active protein malnutrition. However, human milk, in spite of its relatively low protein content, is perhaps the best food and insurance against kwashiorkor and related manifestations of protein malnutrition. The Nutritional Conference in Africa, and a similar Conference again held under the auspices of WHO/FAO in November 1953 in Jamaica, strongly recommended prolonged nursing periods, up to 2 years, as the best available preventive measure against kwashiorkor. This seems to place human milk in a special category of foods. Yet, no conclusive evidence exists showing that the amino-acid composition or the better digestibility of the protein in human milk can explain the superiority of human milk as a source of protein.

Bifidus Factor

Our recent studies on a new microbiological growth factor, for which human milk represents one of the best sources in nature, may have some bearing on the better utilization of human milk protein. This factor is an essential nutrient for a special strain of *Lactobacillus bifidus*, called Penn variant, which was isolated in our laboratory at the University of Pennsylvania. Chemically, the microbiological growth factor is not yet fully characterized. It appears to belong to the group of N-containing polysaccharides with high hexosamine content. It may occur in small or large molecular form. Bifidus Factor activity is found in many mucinous epithelial secretions. The high molecular compounds with Bifidus Factor activity exhibit also, as a rule, blood group activity. For instance, hog mucin, from which blood group A is prepared, is a good source of the Bifidus Factor. Eluates prepared from charcoal columns on which previously deproteinized human milk was adsorbed, also showed high Bifidus Factor activity, but in this case with low or no blood group titer.[1–6]

We studied the effect of hog mucin and of eluates prepared from human milk on the growth of rats. We fed them a ration of cow's milk dilution, which resembled human milk in its composition of total protein, and its fat and sugar content.[7] Both hog mucin and the fractions obtained from human milk, when added to the cow's milk dilution in a concentration sufficient to equalize the microbiological activity of human milk, have proved to have significant growth-promoting effect in rats. Glucuronolactone or galacturonic acid or pectin were unable to replace hog mucin. It is highly probable but not proved that such growth promotion indicates better utilization of protein in a low-protein basal diet. It is interesting to note that similar results were also obtained when hog mucin was added to a high protein diet, provided the protein was of plant origin and of low quality—such as peanut meal, which is low in methionine (Table I).

Lactose in high concentration is known to be injurious to rats. Perhaps the pediatrician feels the impact of this statement more than the general biochemist. According to our own experimental studies and those of Tomarelli and his associates,[8] this deleterious effect, appearing in rats fed a ration high in lactose, may be considerably alleviated. Moreover, an

TABLE I

Effect of Hog Mucin on Weight Gain in Rats Fed an Alipotropic Peanut Meal Ration for 200 Days

Days		Animals	Starting wt.,	Final wt.,	P	Food intake avg. daily
			Gm.	*Gm.*		*Gm.*
200	Control	10	115.0 ± 3.0	292 ± 12.5	—	10.6 ± 0.3
	Hog mucin:					
	25 mg./day	10	115.7 ± 1.9	323 ± 6.0	0.05	10.7 ± 0.4
	50 mg./day	9	115.4 ± 1.8	330 ± 8.1	0.02	10.7 ± 0.4

improved growth-rate will be obtained when hog mucin is added to a diet high in lactose.

The improvment may be due to better protein utilization, or perhaps it may be secondary to the better assimilation of the disaccharide lactose. There are indications in the recent biochemical literature that N-acetylglucosamine may be a part of a coenzyme required for the metabolism of galactose. The polysaccharides in hog mucin and in the human milk fractions are rich in N-acetylglucosamine. The proper role of the Bifidus Factor in these reactions and in the growth promotion exerted by hog mucin or by human milk fractions in the examples mentioned, remains to be elucidated.

Liver Disease

The liver is the central organ of protein metabolism. Protein malnutrition leads not only to a fatty liver, but in addition appears to promote more pronounced pathologic alterations of the liver. Cirrhosis of the liver is a common disease in tropical countries. In Uganda, British East Africa, Davies, after about 5000 autopsies on African natives, has yet to find a normal liver[9]. In Jamaica, there is a great deal of infantile cirrhosis with ascites; there, it is always believed that the cause is due to protein deficiency. In India, a toxic, postnecrotic cirrhosis is found in children. This liver pathology has no bearing on malaria, intestinal parasites, syphilis, or other infectious diseases as such. The cirrhosis is found concomitantly with general malnutrition, which is usually based on a low intake of protein, particularly of animal protein.

Our knowledge and understanding of dietary liver injury was strongly supported by experiments on animals. And we know that it is the rule and not the exception that observations produced from animal experiments may be applied directly, or with minor corrections or variations, to equivalent conditions in human disease. The successful transference of conclusions reached in animal experiments to the clinic presupposes, in its first phase, the experimental production of the disease in question. Once this goal is attained, the etiology and pathogenesis of the disorder, as well as its prevention and therapy, may be studied under exact and well-controlled experimental conditions on a large number of animals. Unfortunately, clinical data suffer because of the shortage of available patients, or at least from the difficulty of maintaining controlled conditions.

Four outstanding results emphasize the developments of the experimental approach to diseases of the liver during the past fifteen years: (a) the recognition of purely nutritional factors as important determining causes of hepatic injury; (b) the prevention, arrest, and even possible reversal of this pathologic process simply by proper changes in the composition of the experimental diet; (c) the interrelationship between dietary and endocrine factors in the pathogenesis of hepatic injury; and (d) the concept that experimental dietary injury to the liver is often combined in the same animal with specific manifestations in the kidney, in particular with acute necrotizing nephrosis.

Dietary factors determining experimental liver injury in rats are summarized in Table II.

Lipotropic Factors

The dietary factors beneficial in the prevention of cirrhosis, which represents the more

TABLE II

Dietary Factors in Liver Injury

	Cirrhosis	Necrosis
Protein	Beneficial	Beneficial
Methionine	Beneficial	Beneficial
Cystine	Injurious	Beneficial
Choline	Beneficial	No effect or injurious
Vitamin E	No effect	Beneficial
Dietary Fat	Injurious	No effect or injurious
Vitamin B_{12}	Beneficial	No effect

chronic form of hepatic injury, may be identified by one common denominator, i.e., a sufficient supply of lipotropic factors, in particular of choline and its precursors. The benefit seen after administration of vitamin B_{12} may be due to its choline-sparing effect. In more recent studies, we found hog mucin effective as a lipotropic agent, and also in the prevention of dietary hepatic cirrhosis (Tables III and IV). Here again, mucin appears to improve protein utilization. Hydrolyzed mucin is inactive as a lipotropic agent, as well as a source of the microbiological Bifidus Factor. However, from this statement one should not infer that Bifidus Factor and lipotropic activity are referred to the same substance.

The first noticeable change resulting from a deficiency of choline and its precursors, such as methionine or methionine-containing protein, is fatty infiltration. This is followed by diffuse fibrosis, and may terminate in the well-known picture of cirrhosis with all its various pathologic attributes. The sequence of fatty infiltration and cirrhosis does not necessarily imply that there is a direct causal relationship between fat infiltration and diffuse fibrosis. A fatty liver may exist for years, for instance, in diabetes in man, without being followed by cirrhosis.

Rats kept on an alipotropic diet develop a fatty infiltration of the liver, which starts in the central zone and rapidly extends over the whole lobule. As Hartroft has clearly illustrated,[10] neighboring hepatic cells with accumulated intracellular fat may coalesce, forming multinucleated fatty cells of varying size producing with further coalescence true "fat-abscesses." The content of such abscesses may be discharged after rupture and flow into the bile canaliculi or into the sinusoids. In the latter case, small fat emboli are found in many organs (kidney, lungs, heart muscle, etc.). Proliferation of connective tissue follows, with disruption and finally complete destruction of the normal hepatic architecture: The result is the well-known picture of hepatic cirrhosis.

In the absence of choline, fat infiltration of the renal tubuli may develop simultaneously

TABLE III

Lipotropic Effect of Hog Mucin in Rats

	Weight change	Food intake	Liver	
			Fresh weight	Total fat
	Gm.	*Gm./day*	*Gm.*	%
Controls	-11.0 ± 2.8	5.8 ± 0.15	5.4 ± 0.5	29.0 ± 3.1
Hog mucin (50 mg. daily)	-11.6 ± 3.5	5.6 ± 0.1	4.9 ± 0.35	15.7 ± 1.7

Ten rats in each group.

TABLE IV

The Effect of Hog Mucin on the Development of Liver Cirrhosis in Rats

Supplement	Weight change	Food Intake	Cirrhosis		Necrot. nephrosis	
			0	+	0	+
mg./day	*Gm.*	*Gm./day*				
—	$+177 \pm 12.5$	10.6 ± 0.35	0	10	1	9
Hog mucin						
25 mg.	$+208 \pm 6.0$	10.7 ± 0.4	3	7	4	6
50 mg.	$+215 \pm 8.5$	10.7 ± 0.35	6	3	8	1

with fat infiltration of the liver, indicating that this disturbance may not be due to blocked transport of fat from the liver but is probably related to a cellular disarrangement of fat metabolism in the hepatic lobules and renal tubules. The changes in the kidney may culminate in severe cortical hemorrhagic necrosis. In young weanling rats, such symmetrical cortical hemorrhagic necrosis of the kidneys occurs regularly and very early in deficiency of choline and its precursors (methionine). In adult rats, this same fatal complication is rarely observed, but may be provoked by starvation interrupting a choline-deficient regime.

Recently, Best, Hartroft, and their associates[11] have demonstrated that choline deficiency, especially when associated with a diet high in fat, may also lead to necrotic and fatty changes of the myocardium and to necrosis and calcification in the media and to a lesser degree in the intima of the aorta and large arteries. The relation of these findings to human arteriosclerosis and cardiomuscular changes is obscure and probably not too close.

Copeland and Salmon[12] described the occurrence of malignant hepatoma in rats kept on a choline-deficient diet. In our own extensive studies, carried out in collaboration with Dr. H. Goldblatt over the past fifteen years, we have encountered hepatoma in rats fed a diet low in casein as a basal ration. However, we found definite indications for the interaction of some "toxic" factors in the peanut meal ration used by Copeland and Salmon. As signs of such toxic effects we have seen widespread small foci of necrosis in the liver lobules, accompanied often by pericholangiolitic changes In general, it may be assumed that all necrogenic hepatotoxic agents are potential carcinogens for the liver. Increased protein intake and perhaps sparing of methionine by an increased supply of choline when a choline-deficient ration is used, may neutralize this toxic carcinogenic effect. In applying these experimental findings to man, it is perhaps justifiable to relate the high incidence of primary hepatoma, in countries where protein malnutrition is widespread, to a combination of protein deficiency[13] with some simultaneous "hepatotoxic" constituent present in the diet.

The acute form of experimental dietary hepatic injury is characterized by massive, often hemorrhagic, necrosis. This form of acute massive dietary necrosis of the liver may be prevented by the sulfur-containing amino acids or by vitamin E. The so-called "Third Factor" of K. Schwarz,[14] which is apparently different both from the sulfur-containing amino acids and from vitamin E, and which is present in yeast, also has a definite preventive effect on this form of dietary massive necrosis of the liver.

In contrast to cirrhosis, it is difficult to reconcile pure deficiency as the possible cause of dietary hepatic necrosis, with the prevention of this condition by substances chemically as different as the sulfur-containing amino acids, cystine or methionine, and the fat-soluble vitamin E. The assumption has been made that the beneficial effect of the sulfur-containing amino acids and tocopherol is more apt to be due to an underlying detoxifying mechanism than to the furnishing of a deficient nutrient. Both vitamin E and the sulfur-containing amino acids are known detoxifying agents which may counteract, through retardation of oxidation, the noxious effect of hepatotoxic and related substances. In the case of dietary hepatic necrosis, such toxic substances may originate in intermediary metabolism or under the influence of the intestinal flora, particularly in the large intestine.

Bacterial Flora

Our first approach was directed toward the elimination, or at least modification, of the intestinal flora as a possible source of factors injurious to the liver. It has been shown that Aureomycin,® when added to the necrogenic experimental basal diet, containing yeast as the sole sourse of protein, had a significantly beneficial effect in the prevention of experimental hepatic necrosis in rats. In contrast to vitamin E or the sulfur-containing amino acids, cystine or methionine, which as supplements to the basal experimental diet will permanently prevent the production of hepatic necrosis, aureomycin was found to delay, as

a rule, the appearance of necrosis. Thus its protective action was only temporary.

If the effect of aureomycin is mediated by the suppression of the intestinal flora, other antimicrobial agents should also prove to be effective. Although not necessarily equal to aureomycin, the effectiveness of other antibiotics depends mainly on their bacterial "spectrum" and possibly also on the ease with which they may produce resistant strains. Thus, it seemed advisable to study the effect of various antimicrobial agents on the production of dietary hepatic necrosis, especially in comparison with the effect of aureomycin.

In one of the experiments we compared aureomycin with polymyxin and streptomycin, and found polymyxin ineffective, streptomycin slightly effective, and aureomycin very significantly effective.

In addition to polymyxin, chloramphenicol and bacitracin were ineffective in the prevention of dietary hepatic necrosis in rats. Sulfaguanidine was slightly effective in its protection, whereas streptomycin, Neomycin,® and Terramycin® were definitely effective in increasing order.

Ingested streptomycin is absorbed from the intestinal tract only in traces. Thus, its beneficial effect in the prevention of hepatic necrosis suggests that its mode of action is by suppression of the intestinal flora. Observations with penicillin agree with this theory. Penicillin when given by injection was either without any, or of only limited beneficial effect. When given by mouth, especially in its poorly soluble organic base salts, it exerted a very marked protection, equal to that of aureomycin.[15,16]

During the first year and a half of this study most of the experiments were conducted with aureomycin. In this period, the delaying effect of aureomycin on experimental hepatic necrosis became gradually less pronounced with successive experiments. The results recorded suggest the conclusion that the average survival time of rats kept under *identical* conditions and fed aureomycin in addition to the necrogenic diet has been considerably reduced, whereas in the same time the survival of the control rats (not receiving aureomycin) remained practically unchanged (Table V).

TABLE V

Exp.	Date	Survival time in days (avg.)	
		Control	Aureomycin®
1	November 1949	34	110
2	January 1950	41	103
3	August 1950	34	58
4	October 1950	32	42
5	January 1951	27	34

During the whole experimental period the same strain of rat (Sprague-Dawley), with the same average initial weight, and with the same experimental diet, was used. Batches of aureomycin from 1949 were compared with more recent batches, and the same reduction in the survival time of the treated rats was obtained with "old" and "new" aureomycin.

In January 1951, when the aureomycin effect seemed to escape us, experiments with the identical strain of rats, and the identical experimental diet (containing ingredients from a common source), were set up by us in two other laboratories, in which similar experiments had never before been conducted. In both these new laboratories the original long and very significant delay in the development of hepatic necrosis by aureomycin was again observed. Furthermore, the survival time of the control rats not receiving aureomycin was also significantly prolonged, compared with the figures given in the last table. These results appear to illustrate that the effect of aureomycin and of other antibiotics on the delay of dietary hepatic necrosis is mediated not primarily and directly through alteration of the metabolism, but only secondarily through the external environment such as the intestinal flora.[17]

Since early 1951, more effort has been made to conduct the experiments under stricter hygienic conditions. Under these improved conditions, and with a new batch of yeast as a constituent of the basal diet, we observed a slight prolongation of the survival time for the control rats and very pronounced protection with oral penicillin, aureomycin, and terramycin.

We also studied the effect of aureomycin, terramycin, and penicillin in the production of

fatty liver and dietary cirrhosis in rats fed a cirrhosis-producing ration. In such rats, aureomycin and terramycin exerted a very pronounced lipotropic effect (Table VI).[16]

TABLE VI

Treatment	Total liver fat	Food intake
	%	*Gm./day*
	25.4 ± 2.0	6.5 ± 0.2
Aureomycin®	12.2 ± 2.2	6.1 ± 0.2
Terramycin®	8.8 ± 0.7	6.7 ± 0.2
Methionine	13.2 ± 2.4	6.6 ± 0.2
Aureomycin + Methionine	7.5 ± 0.7	6.0 ± 0.2
Terramycin + Methionine	7.6 ± 0.9	6.0 ± 0.3

Aureomycin had a highly protective effect on dietary cirrhosis and its sequelae, such as ascites and renal injury (Table VII).

TABLE VII

No. of rats	Sex	Diet	Avg. wt. gain	Cirrhosis
10	M	Y5H	−41.2 ± 11.0	9
10	M	Y5H + A	+16.3 ± 6.5	0
10	F	Y5H	−34.8 ± 6.4	10
10	F	Y5H + A	+19.6 ± 3.6	2

Similar results were obtained with penicillin mixed with the food, either in the form of the potassium salt or a slowly soluble organic basic salt (benzethacil). In contrast to its ineffectiveness in the prevention of dietary massive necrosis of the liver, chloromycetin was found to be beneficial when added to a cirrhosis-producing diet containing peanut meal and a small amount of casein (Table VIII).[18]

The nutritional effect of antimicrobial agents when added to the necrogenic or cirrhosis-producing diet was not limited to the delayed appearance of hepatic necrosis or cirrhosis, but it manifested itself also in promotion of growth. During the last few years, the growth-promoting effect of antibiotics has been successful when tested practically in animal husbandry and is generally considered to be mediated through the intestinal flora.[19]

Germ-Free Animal

We tested the working hypothesis on the toxic etiology of massive dietary necrosis of the liver in germ-free rats fed the usual necrogenic experimental diet. It seemed that the toxic products may have originated in the intestinal lumen through metabolic activities of the intestinal bacteria, or through direct bacterial invasion of the liver. These experiments were carried out in the Germ-free Life Laboratory of the University of Notre Dame, in collaboration with Professor J. A. Reyniers and Dr. T. D. Luckey.

Germ-free rats and conventional control animals were fed the same autoclaved necrogenic diet with yeast as the sole source of protein. The control animals were kept in "normal," non-germ-free laboratory surroundings. All control rats died with massive hemorrhagic necrosis of the liver. In contrast, the

TABLE VIII

The Effect of Antibiotics on the Development of Liver Cirrhosis in Rats Fed Peanut Meal Diet (Experimental Period 150 Days with 10 Rats in Each Group)

Group	Supplement	Weight		Cirrhosis		Kidney injury	
		Starting	Final	0	+	0	+
	mg./day	*Gm.*	*Gm.*				
1		154 ± 2.7	252 ± 19.1	2	8	4	6
2	Aureomycin, 5	154 ± 3.0	310 ± 7.8	8	2	8	2
3	Aureomycin, 25	154 ± 2.7	307 ± 6.2	10	—	10	—
4	Terramycin, 5	154 ± 2.4	305 ± 6.1	8	2	8	2
5	Terramycin, 25	152 ± 2.2	327 ± 4.6	10	—	10	—
6	Penicillin, 25	153 ± 1.8	307 ± 3.3	10	—	10	—
7	Dibenz. Pen., *5	153 ± 2.1	325 ± 2.7	10	—	10	—
8	Dibenz. Pen., 25	153 ± 2.3	320 ± 5.8	10	—	10	—
9	Chloromycetin, 5	152 ± 2.0	307 ± 10.0	7	3	9	1
10	Chloromycetin, 25	152 ± 1.9	309 ± 5.5	10	—	10	—

* Benzethacil (dibenzylethylenediamine dipenicillin).

germ-free animals lived twice as long as the experimental animals and at autopsy showed no necrosis of the liver. Their weight curve throughout the whole experiment was very satisfactory, in contrast to the flat curve of the conventional, non-germ-free control animals.

The food intake of the germ-free rats was, under the conditions of *ad libitum* feeding, much greater than that of the conventional controls. When in further experiments the food intake of the germ-free and control animals was equalized through pair-feeding, massive necrosis of the liver developed in the germ-free animals, although with a definite delay when compared with the appearance of massive necrosis in the conventional control animals. Thus, bacteria are not essential etiologic factors in the development of dietary massive necrosis. The observations in germ-free animals and in conventional rats on antibiotics are in better accord with the assumption that bacteria in the intestinal tract may use up protective constituents of the food ingested and in consequence reduce their supply for the body.

Choline

Sparing of an essential dietary constituent under the influence of antibiotics has been recently demonstrated by Popper and his associates in the case of choline.[20] Two-thirds of ingested choline is excreted by a normal person in the urine as trimethylamine or its oxidized form. Priming with aureomycin or penicillin will reduce to very low levels the excretion of trimethylamine after ingestion of choline. The intravenous injection of choline will not lead to urinary excretion of trimethylamine. These observations seem to indicate that the intestinal flora even in a normal person may convert large proportions of choline into trimethylamine. Suppression of the intestinal flora or at least of its choline-metabolizing constituents by aureomycin or penicillin will make more choline available for the body. By analogy, similar mechanisms may be postulated for other lipotropic food constituents, such as methionine, effective in the prevention of dietary cirrhosis.

However, such a simple solution is not borne out by more intensive analysis of all participating factors. In the first place, in collaboration with Popper and his associates,[21] we found that the sparing of dietary choline under the influence of aureomycin and penicillin is only a very temporary effect, lasting only a few days. In spite of continuous medication with antibiotics, the original high excretion of trimethylamine re-established itself as observed before antibiotics were given. In view of the fact that cirrhosis-prevention may last for 150–200 days, the short-lived sparing effect, at least as far as demonstrable, is not sufficient to explain the beneficial result which follows prolonged administration of antibiotics.

Furthermore, in intensive studies we were unable to demonstrate any permanent change in the composition of the intestinal flora as the result of antibiotics' action.[22] Temporary suppression of sensitive micro-organisms is followed by the return of the original flora characteristic for the diet in question. The only difference is the emergence of resistant strains. Thus, it is our present assumption that all the metabolic changes, such as prevention of hepatic injury or growth promotion, must be linked with an altered metabolism of the micro-organisms comprising the symbiotic intestinal flora. There are indications that such changes may be reflected in the metabolism of the host organism as well.

Urine Acids

We found an especially promising lead through the study of ether-soluble acids (ESA) in the urine. Rats fed the necrogenic experimental diet have a lower total ESA excretion than rats fed the same diet supplemented with aureomycin or penicillin. We found through chromatographic analysis a particular, not yet chemically identified, ether-soluble acid in the urine of experimental animals receiving aureomycin and penicillin. There are other marked differences in the excretion of ESA in the urine of supplemented and unsupplemented rats. The possible relation of these findings to the effect of antibiotics on the liver and growth is obvious but requires further intensive study.[23]

Other Studies

In a recent study we divided rats, all fed the usual experimental diet, into three groups. The first large group was used as control; the other two groups received the same diet supplemented with aureomycin and penicillin, respectively. After about four weeks, the first large control group was subdivided into three subgroups: one was left without supplement, the remaining two subgroups were given aureomycin and penicillin, respectively. Whereas most of the rats receiving the antibiotics from the start survived 200 days, there was no significant prolongation of survival time in the groups with late addition of the antibiotics when compared with the controls. This observation further supports the theory that antibiotics act not by suppression of infection or of bacterial action alone, but probably more by sparing of important protective food constituents (Table IX).[18]

We return now to the question of how far these experimental observations apply to conditions in man, with special reference to the problem of protein malnutrition, and in particular to the problem of kwashiorkor.

Admittedly, a diet low in protein may lead to severe liver injury. However, the classical clinical picture of kwashiorkor is not reproduced when a ration low in protein is used, as in the example of casein fed to rats. Further, some objection has to be raised to the statement that kwashiorkor should be more closely related to the mathematical equation of a relatively low proportion of protein-calories to the total consumed calories per day, than to the theory of mere protein undernutrition. This statement is at variance with observations in animals and man, which have clearly demonstrated that the utilization of protein can be improved, even with a low absolute intake of protein, by an increase of nonprotein calories in the diet.

Quality of Protein

There is some experimental evidence in support of the hypothesis that a disturbed equilibrium of amino acids, or, more descriptively, the inclusion of plant proteins in the diet, is probably of major etiologic importance in the development of protein malnutrition such as kwashiorkor Engel and his associates produced severe generalized edema, with hypoalbuminemia, fatty liver, and cirrhosis in rats. They employed a ration containing 7 per cent protein, furnished mainly in the form of peanut-protein, and supplemented with a small amount of casein.

If protein deficiency is produced by a diet low in casein, the demonstrable manifestations are confined mainly to the liver and the kidney. Neither generalized edema nor pancreatic changes, both important characteristics of kwashiorkor, are found as a rule in rats fed

TABLE IX

The Effect of Continuous, Delayed, or Alternating Administration of Antibiotics on the Development of Massive Dietary Hepatic Necrosis*

Group	Supplement	No. of rats	Died with hepatic necrosis	Average survival time	Survived 150 days without hepatic necrosis
A	—	10	10	23 ± 0.8	—
B	—	8	8	34 ± 1.3	—
C	Nothing for 26 days, then Bicillin®	11	10	44 ± 7.6	1
D	Nothing for 26 days, then aureomycin	11	9	50 ± 9.0	2
E	Aureomycin	10	4	54 ± 8.5	6
F	Aureomycin for 44 days, then bicillin	10	4	63 + 5.0	6
G	Bicillin	10	2	42 ± 0.0	8
H	Bicillin for 42 days, then aureomycin	10	2	112 ± 2.0	8

* Average starting weight of animals in all groups, 49 Gm.

a diet low in casein, as the only protein constituent.

However, ethionine, the analogue and probable metabolic antagonist of methionine, produces fatty liver and severe pancreatic changes through disturbed protein synthesis.[24] This again raises the question of toxic factors. Infantile cirrhosis in India and severe hepatic injury in infants in Jamaica are reminiscent of so-called toxic cirrhosis. In Jamaica, infants after weaning are fed a low protein diet; in addition, they are offered, fairly regularly, decoctions of native plants, in the form of so-called bush-tea. As recently shown by Bras,[25] the liver changes of the Jamaican type of infantile cirrhosis are based originally on vascular obstruction, through endothelial edema and proliferation of the hepatic venules and veins. It is of great interest that similar changes may be experimentally produced in rats fed a low protein diet supplemented with an extract of senecio discolor. Here we are dealing with the combination of protein undernutrition and toxic effect.[26,27]

It is possible that the nature of nonproteinaceous food constituents, such as starchy foods, may also influence protein utilization.

Clinical Considerations

In general, preventive and therapeutic measures are by no means necessarily interchangeable. In the example of pathologic hepatic conditions, for example, effective prophylactic factors should and will prevent the development of the major specific metabolic and anatomical changes. Therapeutic efforts, on the other hand, have to deal with the arrest or even regression of already existing metabolic and anatomical changes. For instance, in the case of cirrhosis the progress of fibrosis has to be checked or even reversed, in addition to repair of all other concurrent pathologic disturbances. Furthermore, in cirrhosis not only the liver but often other organs as well, such as the kidneys and endocrine glands—especially the gonads—are found to be involved in the overall disease. As a consequence, the dietary treatment of severe malnutrition is often not as successful as its prevention.

Protein malnutrition and its clinical sequelae, including liver disease, are a serious world-wide problem with important political implications. Improved health achieved by improved nutrition and the prevention of liver disease, will give tropical populations a better balance of physical and mental abilities, improve their general outlook on life, and assure them a healthier future. The task is difficult, but its success is worth the effort.

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Resumen

Sobre algunos aspectos de la nutrición proteica

La malnutrición proteica es un problema mundial. En los países tropicales esta condición se designa con el nombre de kwashiorkor; clínicamente es semejante si no idéntica a "Mehlnärhschaden" o disergia farinacea, vista en la Europa post-bélica.

En la malnutrición proteica el consumo diario de calorías totales no es gravemente reducido; es más bien la relación de las calorías proteicas a las calorías totales que es reducida. Si ésta desciende por debajo de un 10 por 100, manifestaciones clínicas de deficiencia proteica han de atenderse. En la leche humana, sin embargo, la relación de las calorías proteicas a las calorías totales no es más de 6 a 7 por 100—pero la leche humana constituye la mejor protección contra el kwashiorkor y se recomienda el amamantiamento prolongado para evitar esta condición en las regiones afectadas. La presencia en leche humana del *factor bifidus* (un nuevo factor microbiológico de crecimiento) puede constituir una explicación parcial de la mejor utilización de la proteína en leche humana y así de este hecho paradójico.

El hígado es el órgano central del metabolismo proteico, y el daño hepático se halla comunmente donde el consumo de proteína—sobre todo de proteína animal—es escaso. El papel desempeñado por los factores nutritivos en la causa, profilaxis y resolución del daño hepático se ha confirmado de modo impresionante por la experimentación animal. Le presencia de una suficiencia de factores lipótropas (especialmente de la colina y sus precursores) protege contra la forma crónica de daño hepático (cirrosis). La forma aguda (necrosis masiva) se puede prevenir por los aminoácidos sulfúreos, la vitamina E, o el llamado "tercero factor" de Schwarz, presente en la levadura. Se discuten los papeles respectivos de deficiencia y toxicidad en la necrosis. Con este motivo se refieren experimentos con varios antibióticos en la protección contra la necrosis y cirrosis. Los resultados sugieren que la flora intestinal puede, por consumir factores nutritivos protectivos, reducir su disponabilidad al organismo. La colina, por ejemplo, se ha demostrado ser mejor utilizado cuando se suprime a la flora intestinal—o por lo menos a esos constituyentes que metabolizan a la colina—con aureomicina o penicilina. Este

efecto, sin embargo, parece ser temporal, y conviene estudiar el fenómeno más a fondo.

Se examina la aplicabilidad a la nutrición clínica de estos diversos hallazgos experimentales. Se insiste en la profilaxis por el mejoramiento del régimen, pues el tratamiento dichoso de la malnutrición severa, repercutiendo sobre muchos órganos, es a menudo cosa difícil. La salud de los indígenos de los trópicos, en particular, depende de la solución del problema nutricional y la profilaxis de la hepatopatía.

Food and Civilization

"The essential material foundations of civilization are cereal and livestock farming and improving both plants and animals. Man did not or could not develop the arts and technology of civilized life until he passed from food-gathering cultures to the food producing stage. . . .

"Civilization cannot exist without food production, but food production must be very efficient before civilization can begin. The transition from primitive to civilized life has happened more than once, but Mesopotamia and Egypt were the first cultures to rise above primitive existence. . . .

"It is to be understood that the transition to food production between seven and eight thousand years ago occurred in certain favored areas of the world only, and is still not completely achieved. Globally the goal has not been reached. Some of the human family are still in middle Pleistocene stages in their sustenance patterns. Efficient production and food preservation and storage determine to a large extent man's victory over Nature."

—L. B. Jensen. *Man's Foods,* The Garrard Press, Champaign, Ill., 1953, pp. 41, 47, 48.

The Sociology of Nutrition

"Audrey Richards (1948), in her studies on hunger and work in a savage tribe, observed that nutrition as a biological process, i.e., sociological process, is more fundamental than sex. Professor Malinowski . . . agreed wholeheartedly that this is the case in both primitive and highly developed cultures. The over-emphasis on sex (and neglect of other appetites, drives, and interests) has in previous studies obscured the issue. Furthermore, according to Professor Malinowski, commonsense tells us that nutrition is an independent impulse. The drives of hunger and appetite, and the bonds of co-operative economic interests and commensualism, both in Paleolithic and Neolithic times, stem from nutrition. . . . Dr. Richards finds, as biochemistry has long taught, that nutrition in a primitive tribe is a single process, from suckling, or lactation, and family life continuing through the period of full economic status of the adult. Obviously, there is nothing more important to man than what he eats and how he eats.

"The importance of nutrition as a social activity is well attested by both ancient and modern thinkers, and present-day biochemical data, so great in detail and so rapid in advance, extend the overwhelming importance of proper diets to man, the individual, and his cultures. Lord Boyd-Orr and many others point out that malnutrition of the East and opulence of the West must lead to conflict if not corrected in time."

—L. B. Jensen. *Man's Foods,* The Garrard Press, Champaign, Ill., 1953, pp. 148–149.

The CYSTINE *and* METHIONINE *Content of the Hair of* MALNOURISHED CHILDREN

By ALICE P. WYSOCKI,* GEORGE V. MANN, M.D.,† AND FREDRICK J. STARE, M.D.‡

THE EXTENSION of medical care and observation to primitive areas of the world has emphasized the importance of the striking human weanling disease described for western medicine by Williams[1] and called *kwashiorkor*. This name, a West African dialect word for "red boy," describes the characteristic reddening of the skin and hair seen in dark-skinned children.

Kwashiorkor has now been described in many parts of the world[2] and appears to be a common complication of that crucial dietary transition in a child's development from the mother's breast to solid food. The visceral complications of the disease and particularly the profound alterations of the liver structure are believed to contribute to serious chronic diseases of adult life such as cirrhosis and carcinoma of the liver.[4,5] This residual injury is in addition to the very large mortality occurring in children when the dramatic kwashiorkor syndrome is present.

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Considerable evidence now indicates that kwashiorkor is primarily a nutritional disease.[6] Assessment of previous dietaries and trials with protein supplements have indicated that an insufficient amount of adequate protein in the diet is of first importance in the etiology of kwashiorkor.

It is well known that the eukeratins, of which mammalian hair protein is a representative, contain relatively large amounts of sulfur. This element is largely present as a component of cystine[7] with methionine and perhaps cysteine present in much smaller amounts.[8] It has been shown by Heard and Lewis[9] that the dietary sulfur levels influence the sulfur content and distribution of hair in growing rats.

It occurred to us that the cystine and methionine content of hair from malnourished children might be a sensitive indicator of the presence of kwashiorkor or one of its variants. Aside from the significance such a demonstration would have in revealing the etiology of kwashiorkor, a sensitive hair indicator might also serve to detect the disease before irreparable structural damage had been done. These considerations led us to a study of the content of cystine and methionine in the hair of such malnourished children.

METHODS

During April and May of 1953 approximately 75 hair samples were collected in a number of clinics in Indonesia. The majority were taken in the hospital of the University of Indonesia, Djakarta, and consisted of 10–1000 mg. of head hair obtained from normal

and malnourished children. The nutritional status of the children was classified by the Indonesian physicians on the basis of dietary histories, clinical signs, and laboratory measurements of hemoglobin and serum proteins. The children ranged in age from 8 to 48 months. They were for the most part described as being of Indonesian parentage, but a few were of Chinese ancestry.

Analysis of Hair

When the hair samples were received in Boston, they were defatted, dried to a constant weight, hydrolyzed with hydrochloric acid, and analyzed for methionine and cystine.

Fat Extraction: Each sample was rolled into a circle of Whatman #1 filter paper and the ends secured by stapling. The package was immersed in Bloor's solution (ethanol-ethyl ether 3:1) for 48 hours at room temperature. The solvent was renewed at the end of the first 24 hours.

Drying: The samples were air-dried for 72 hours at about 60° C. They were then placed in loosely corked plastic tubes and stored in a desiccator over phosphorus pentoxide.

Weighing: The tubes were then tightly stoppered and removed for weighing on each of at least three consecutive days. When a constant weight was reached, the contents of the package were emptied into a hydrolyzing flask. This was done by cutting the ends of the paper tube and allowing the hair to slide into the flask. The paper and the cut ends were returned to the original drying tube and weighed immediately and on at least three successive days. The weight of the hair sample analyzed was thus obtained by difference.

Hydrolysis: The hair was placed in a flask fitted with an air condenser and containing a 1:1 mixture of 20% hydrochloric acid and 88% formic acid. The volume of acid used depended on the weight of sample, but varied from 6–20 ml. for sample sizes of 200–1000 mg. The hair was refluxed for approximately 12 hours at 120–125° C. The resulting hydrolysate was transferred quantitatively to a porcelain evaporating dish and concentrated to a thick syrup on a steam bath. This was taken up in water and filtered through paper. The filtrate and washings were brought to a convenient volume with 0.1 *N* hydrochloric acid. Aliquots of this material were used for analysis.

Cystine analysis was by the Block and Bolling adaptation of the Winterstein-Folin procedure[10] and methionine was measured by the method of Horn, Jones, and Blum.[11]

Results

The analyses were successfully completed on hair samples from 40 children. The remaining samples, thought to be from children who did not have the kwashiorkor syndrome, furnished too little material for analysis. Of the 40 samples considered here, seven were from normal Indonesian children and 33 were from children classified as haying kwashiorkor. The data obtained are shown in Table I, which gives a statistical summary of the findings. Inspection of this table reveals that there was no significant difference between methionine and cystine content of hair from normal or malnourished children. While the variation of the methionine content among children was large, as is indicated by the standard deviations in Table I, inspection of the data of individuals failed to reveal evidence that the hair composition was related either to the clinical description or to the laboratory measurements of hemoglobin, serum total protein, albumin and globulin which had been carried out in the Indonesian hospitals.

Since kwashiorkor, like many other nutritional diseases, appears to be the consequence of long continued dietary inadequacies, it is

TABLE I

The Methionine and Cystine Content of the Hair of Normal and Malnourished Indonesian Children

	Age, months, mean and standard deviation	Methionine as % of dry hair weight ± standard deviation	Cystine as % of dry hair weight ± standard deviation
Normals (7 females)	19.4 ± 9.5	0.641 ± .141	15.27 ± .797
Kwashiorkor (22 females)	22.4 ± 9.0	0.784 ± .259	15.01 ± 1.92
Kwashiorkor (11 males)	22.4 ± 9.7	0.793 ± .289	15.08 ± 2.09

proposed that changes of hair composition might require long periods of malnutrition for development. Thus, older children with longer exposure to the adverse dietary might reveal hair changes not seen in the younger children. Charts relating the hair content of both cystine and methionine to the age of the sick children were made, but these failed to reveal a meaningful relationship. Thus, the older children showed no progressive deviation from the control levels. Neither could a sex difference be demonstrated in this respect.

We conclude that kwashiorkor is not characterized by an abnormality of hair content of cystine and methionine. The structural changes of hair observed in kwashiorkor would appear to represent either a total inhibition of growth or a deviation of some other constituent than the sulfur-containing amino acids.

The observations of Dean[6] which indicate that leguminous foods may have a curative action when administered to children ill with kwashiorkor also argue against the disease being a sulfur deficiency, for pea and soybean proteins are notably lacking in cystine and methionine.

Summary

Chemical analysis of hair samples of 33 Indonesian children with kwashiorkor failed to reveal alterations of the cystine or methionine content.

Acknowledgments

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Resumen

El contenido de cistina y metionina de los cabellos de niños malnutridos

El análisis químico de muestras de cabellos de 33 niños indonésicos con kwashiorkor no reveló ninguna alteración del contenido de cistina o metionina.

NUTRIENT INTAKE *and* BLOOD FINDINGS *of Men on a* DIET DEVOID OF MEAT

By LEONORA MIRONE, PH.D.*

FOR THE PAST few years this laboratory has been interested in a community of men subsisting on a diet devoid of meat and low in animal protein, fat, and cholesterol. A previous study[1] disclosed that despite the low animal protein intake for periods of from 12 to 47 years, the erythrocyte count, hemoglobin and hematocrit values, blood iron, glucose, nonprotein nitrogen, total serum protein, albumin, and globulin levels were within normal limits. A further study of this community was thought to be of interest. Accordingly, the work and rest habits, the average daily nutritive intake, and the kinds of foods served were studied. Serum cholesterol and cholesterol-ester determinations were made to investigate the effect of a persistently low cholesterol intake on these values. In order to study the effect of low animal protein intake on the nonprotein nitrogenous constituents of blood, determinations of nonprotein nitrogen, urea nitrogen, uric acid, and creatinine levels in the blood were also performed.

WORK, REST, AND FOOD PATTERNS

The community was self supporting. The members of the community were engaged in land reclamation, raising of crops, breeding of dairy herds, construction of living quarters for the men and barns to house animals and crops, making and repair of apparel and furnishings, maintenance of farming tools, and farming. Thus, the men were very active physically. They worked eight hours a day, six days a week at their respective occupation. The men rose at 2:00 a.m. every morning; they retired at 7:00 p.m. during the winter months and at 8:00 p.m. during the summer. In the summer they rested one hour after dinner; thus the men slept or rested 7 hours per day throughout the year. The remaining 9 hours were spent in mental activities and moderately active physical activities.

With few exceptions, all the foods served were raised by the men. All meals were prepared on the premises and were always served at the same hour of the day in a common dining hall. Six and a half months of the year—September 14 to March 30, designated as the first period in this study—the food intake was more restricted than during the remaining five and a half months—April 1 to September 13, designated in this study as the second period. Table I summarizes the meal pattern followed throughout the year.

Meat was never served, nor was meat stock added to the soup. Likewise eggs, as such, were never served; however, 10 ounces of dried eggs (1.36 per cent) were added to a 46-pound batch of raisin bread which was served 28 times during the year. Also, the plain cake or cookies which were served only 10 times during the year contained fresh eggs according to the recipe used. The barley coffee contained 9.26 per cent fresh skim milk, and the whole wheat bread contained 2.17 per cent dried skim milk. Although vegetables and fruit of all varieties were permissible, the variety was limited to a great extent to those crops native to the area in which the com-

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TABLE I

Meal Pattern

Meal	Time	First period: Sept. 14 to Mar. 30	Second period: Apr. 1 to Sept. 13
Breakfast	6:00 a.m.	2 oz. whole wheat bread, barley coffee	6 oz. whole wheat bread, barley coffee
Dinner	12:00 a.m.	Vegetable soup portion, a serving of two vegetables, whole wheat bread, barley coffee	Vegetable soup portion, a serving of two vegetables, a fresh fruit or 2 oz. stewed fruit, whole wheat bread, barley coffee
			Mon. Wed. Fri. & Sat.
Supper	5:30 p.m.	6 oz. whole wheat bread, 2 oz. fruit sauce, barley coffee	Vegetable soup portion, a fresh fruit or 2 oz. stewed fruit, whole wheat bread, barley coffee
		17 Sundays	*Sun. Tues. & Thurs.*
		Milk, skim, American Cheddar Cheese, 3 x 2 x 1/8 portion, whole wheat bread, barley coffee	Milk, skim, American Cheddar Cheese, 3 x 2 x 1/8 portion, whole wheat bread, barley coffee

munity was located. The whole wheat bread was made from wheat grown and milled by the men. A tablespoon of margarine or butter was served 28 times per year. In Table II are summarized the foods served and in some instances the number of times the food was served during the year.

TABLE II

Foods Served

		Occasionally
Vegetables		
Beets	Parsnips	Broccoli
Cabbage	Peas	Cauliflower
Carrots	Pumpkin	Rutabagas
Celery	Potato, Sweet	Sauerkraut
Corn	Potato, White	
Chinese Cabbage	Radishes	
Cucumber	Spinach	
Eggplant	String beans	
Endive	Tomatoes	
Lettuce	Squash, Summer	
Mustard Greens	Turnips	
Onions	Turnip Greens	
Okra		
Legumes		
Navy beans	Lima beans	
Fruit		
Apples	Peaches	Bananas
Cantaloupe	Pears	Blackberries
Figs	Watermelon	Grapefruit
Oranges		Grapes
		Raisins (in raisin bread)
Dairy Products		(*Occasionally*)
Milk, fresh skim and dried skim		
Cheese, American Cheddar		
Bread and Cereals		
Bread, whole wheat	Oatmeal	Corn Bread
Cornflakes	Rice	Raisin Bread (28 times per year)
Macaroni	Spaghetti	
Beverages		
Barley Coffee		Cocoa 10 times per year
		Coffee 15 times per year
Fat		
Wesson Oil®		Oleomargarine or butter 28 times per year
Tastex®-hydrogenated shortening		
Peanut Butter		
Miscellaneous		
Apple Pie, rarely	Ice cream 15 times per year	
Candy, hard or chocolate 30 times per year	Molasses, in raisin bread	
Honey, rarely	Sorghum, rarely	

Experimental Procedure

Six members of the community participated in the study. The men appeared to be "healthy"; they were free of symptoms of illness, considered themselves in normal health, and were actively engaged in their usual activities. However, they were not examined

TABLE III

Personal Data

Case No.	Age entering community	Number of years in community	Present age	Occupation	Height	Body structure	Actual weight	Desirable weight*	Remarks
	yrs.		*yrs.*		*in.*		*lb.*	*lb.*	
1	19	20	39	Farmer	71	Large	169	165–180	
2	21½	19	40½	Lecturer	71	Large	200	165–180	Overweight
3	27	15	42	Carpenter	68½	Medium	160	147–158	
4	20	14	34	Teacher	74	Large	135	179–196	Underweight
5	19	22	41	Laborer	62	Small	140	116–125	Overweight
6	34	17½	51½	Plumber	67	Medium	145	141–151	

* Metropolitan Life Insurance Company: *Desirable Weights for Men of Age 25 and Over.*

clinically. The personal data on the subjects are summarized in Table III.

A three-day weight record of the food intake for each of the two periods was kept for each of the subjects. The average intake for calories, animal protein, vegetable protein, total protein, fat, carbohydrate, calcium, iron, vitamin A, thiamine, riboflavin, niacin, ascorbic acid, and cholesterol was calculated for the two periods for each subject. The nutrients were calculated from standard tables.[2,3] The cholesterol content was calculated from tables by Okey[4] and Ansbacher and Supplee.[5] Vegetable sterols are not utilized in the human body, and therefore they were not included in the cholesterol calculations. In Table IV are summarized the average daily nutrient and cholesterol intake. Fasting blood samples were obtained for both periods. The chemical blood findings are summarized in Table V.

TABLE IV

Average Daily Nutrient and Cholesterol Intake

Case No.	Calories	Animal protein	Vegetable protein	Total protein	Fat	Carbohydrate	Calcium	Phosphorus	Iron
		Gm.	*Gm.*	*Gm.*	*Gm.*	*Gm.*	*Gm.*	*Gm.*	*mg.*
				First Period					
1	2825	12	48	60	21	599	0.70	1.50	14
2	2601	11	51	62	21	541	0.71	1.56	15
3	2070	10	44	54	22	414	0.69	1.39	14
4	2123	10	61	71	27	399	0.76	1.79	18
5	1920	10	35	45	20	390	0.56	1.11	10
6	2395	9	46	55	19	501	0.59	1.38	13
Av.	2326	10	48	58	22	474	0 67	1.46	14
Intake as calories	—	40	192	232	198	1896			
Intake as % of total calories	—	1.8	8.2	10.0	8.5	81.5			
				Second Period					
1	3149	24	51	75	21	665	1.40	1.79	16
2	2080	32	37	69	32	379	1.04	1.64	14
3	2402	16	46	62	22	489	1.13	1.54	16
4	2726	23	82	105	34	500	1.84	1.69	27
5	2477	22	39	61	17	520	1.00	1.51	12
6	2871	23	46	69	19	606	1.26	1.69	15
Av.	2617	23	50	73	24	527	1.28	1.64	17
Intake as calories	—	92	200	292	216	2108	—	—	—
Intake as % of total calories	—	3.5	7.6	11.1	8.3	80.6	—	—	—
National Research Council recommended allowances	2900	—	—	65	—	—	0.8	—	12

TABLE IV (*Cont.*)

Case No.	Vitamin A	Thiamine	Riboflavin	Niacin	Ascorbic acid	Cholesterol
	I.U.	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
			First Period			
1	857	1.8	1.3	15	60	12
2	11,233	2.0	1.4	17	91	11
3	11,383	1.7	1.3	15	86	12
4	11,923	3.5	1.5	20	101	13
5	609	1.3	1.0	11	45	12
5	5,177	1.7	1.1	15	61	9
Av.	6,863	2.0	1.3	15.5	74	11.5
			Second Period			
1	10,388	1.8	2.2	15	135	25
2	1,945	1.5	1.9	12	106	22
3	12,472	1.7	1.8	19	126	21
4	23,362	3.1	3.0	25	213	30
5	365	2.1	1.7	12	78	24
6	7,865	1.3	2.1	14	123	23
Av.	9,399	1.9	2.1	16	130	24
National Research Council recommended allowances	5,000	1.5	1.6	15	75	—

TABLE V

Chemical Blood Findings

Case No.	Total serum cholesterol[a]	Cholesterol ester[b]	Nonprotein-nitrogen[d]	Urea nitrogen[e]	Uric acid[f]	Creatinine[g]
	mg. %	*%[c]*	*mg. %*	*mg. %*	*mg. %*	*mg. %*
			First Period			
1	225.3	63.4	31.8	12.3	2.3	1.8
2	190.7	71.8	31.5	14.9	3.0	1.4
3	210.4	71.5	32.3	15.1	3.8	1.7
4	183.9	68.1	33.6	10.9	4.1	1.2
5	231.8	73.9	25.4	10.1	2.9	1.9
6	202.5	75.0	29.7	13.5	4.0	1.4
Av.	207.4	70.6	30.7	12.8	3.35	1.56
			Second Period			
1	229.0	65.0	35.3	14.5	2.6	1.7
2	190.9	72.3	33.1	15.1	2.9	1.2
3	207.4	69.8	35.0	13.9	4.2	1.7
4	192.3	64.4	29.5	12.9	3.2	1.3
5	235.4	71.9	28.7	10.7	3.0	1.5
6	199.8	68.9	30.0	14.0	3.7	1.5
Av.	209.1	68.7	31.9	13.5	3.26	1.48

[a] Bloor's Method. [b] Bloor and Knudson's Method. [c] Of total cholesterol. [d] Folin-Wu Method. [e] Van Slyke and Cullen's Aeration Method. [f] Modified Kock's Method. [g] Folin Method.

Discussion

It is apparent from Table I that the mainstays of the diet were whole wheat bread containing 2.17% dried skim milk, barley coffee containing 9.26% fresh skim milk, vegetables, and fruit. In addition, it will be noted that small amounts of animal protein, in the form of the skim milk present in the whole wheat bread and the barley coffee were ingested at each of the three meals. According to Leverton and Gram,[6] inclusion of animal protein at

each meal, particularly in cases in which the total protein and caloric intake is low, is essential for maximum nitrogen retention.

The average daily intake of calories, total protein, calcium, and riboflavin for the *first period,* as shown in Table IV, was somewhat lower than the recommended allowances of the National Research Council.[7]

The average daily intake of riboflavin represented 81 per cent of the "recommended" allowance. Williams *et al.*[8] have reported 0.5 mg. of riboflavin per 1000 calories as representing the *minimal* daily requirement for riboflavin. Since the average daily caloric intake of the subjects was 2326 calories, the intake of 1.3 mg. of riboflavin would seem to satisfy the minimal daily requirement.

The average total protein intake was 58 Gm., with an average of 17.2 per cent of the total protein of animal origin. This figure is lower than the recommended allowances for protein and is also lower than the figures reported by Stare and Davidson[9] and Cuthbertson[10] for men.

Due to a paucity of information concerning the human requirement for fat, fat allowances must be based more on eating habits than on physiological requirements. Whereas the National Research Council has suggested that fat be included to the extent of 20 to 25 per cent of the total calories for adults, in this study the average daily fat consumption was only 8.5 per cent of the total caloric intake.

Further study of Table IV will show that with the exception of the caloric intake, the total protein, calcium, and riboflavin during the *second period* (which represented $5^1/_2$ months of the year) were within accepted recommended allowances. This was accomplished by adding to the diet of the first period skim milk as a beverage, cheese, a serving of soup at supper, and larger servings of whole wheat bread at breakfast and supper.

Despite the low fat intake (22–24 Gm. average) and a caloric intake within traditional limits (2326 and 2617 cal.) as shown in Table IV, two of the six subjects (Nos. 2 and 5) were overweight. There are insufficient data to explain this interesting finding.

Cholesterol

Although the cholesterol and fat intake of the subjects was low, the serum cholesterol and cholesterol ester values, as shown in Table V, were within normal ranges. This finding is in agreement with the report of Garn and Gertler[11] that the adult serum cholesterol of Aleuts receiving low calorie, low cholesterol diets did not differ from that of adult Americans. Since in recent years interest in dietary cholesterol has centered on its possible role in the development of arteriosclerosis, it is interesting to note that a low dietary (animal) cholesterol intake maintained over many years was associated with normal blood cholesterol levels.

Blood Findings

An animal protein intake of 10 Gm. for $6^1/_2$ months and of 23 Gm. for $5^1/_2$ months of the year did not produce changes in the nonprotein nitrogenous fractions of the blood. These fractions, as shown in Table V, were within the normal range. This is not surprising in view of the fact that part of the year the total protein intake was within the "normal" range and that the animal protein was distributed throughout the 3 meals.

It appears that although meat adds zest and variety to meals, an adequate diet can be planned in its absence. Prolonged consumption of a vegetable diet which included skim milk was compatible with apparent good health.

Summary

Prolonged consumption of a diet low in animal protein (10–23 Gm.) had no apparent deleterious effect on the health of members of a community which did not eat meat.

The addition of skim milk to a vegetable diet raised the nutritive value of the diet to within accepted standards.

The serum cholesterol and cholesterol ester levels were maintained at normal levels despite prolonged consumption of a low fat, low cholesterol diet.

A diet devoid of meat and low in animal protein had no effect on the nonprotein nitrogenous fractions of the blood.

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RESUMEN

Consumo alimenticio y estudios sanguíneos de hombres consumiendo una dieta sin carne

El consumo prolongado de una dieta pobre en proteína animal (10–23 Gm.) no parece haber tenido ningún efecto deletereo sobre la salud de los miembros de una comunidad que no consumía carne.

La adición de leche descremada a una dieta vegetal aumentó el valor nutritivo del régimen hasta encadrar dentro de los límites aceptados.

El colesterol sérico y los esteres de colesterol se mantuvieron a niveles normales a pesar del consumo prolongado de una dieta pobre en grasas y colesterol.

Una dieta sin carne y pobre en proteína animal no tuvo ningún efecto sobre las fracciones no proteicas de la sangre.

The PROTEIN STATUS in PULMONARY TUBERCULOSIS

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Tuberculosis is so often associated with body wastage that for centuries the terms "phthisis" and "consumption" have been used to describe it. It is therefore extraordinary that it was not until 1903—fifty years after the introduction of the nitrogen balance technique— that May[1] used this method to study protein metabolism in pulmonary tuberculosis. Moreover, although manipulation of the diet has for many years been a major therapeutic measure in managing patients who are ill with tuberculosis, it was only in 1908 that Bardswell and Chapman[2] undertook a systematic study of the effects of different levels of caloric and protein intakes on the course of the disease. From then up to the present, two noteworthy quantitative dietary studies were made in pulmonary tuberculosis. These were McCann's work on patients[3] in 1922 and the investigations of Koerner, Getz, and Long[4] on rats.

There are several rough methods available for assessing the systemic protein status. The loss of weight may be apparent on clinical inspection or determined on a scale. Large weight losses are accompanied by looseness and flabbiness of skin and by poor tissue turgor. Nitrogen balance studies may detect daily losses of nitrogen, and the level at which equilibrium can be achieved may indicate the adequacy of body protein stores. For some time it was hoped that the plasma protein concentration, particularly the albumin level, might serve as a ready and faithful indicator, but recent studies have proved to be disappointing. Thus Keys *et al.*[5a] have shown that the plasma albumin remains within the normal range even when 25 per cent of body weight has been lost. To the above methods may be added changes in the body compartments occurring fairly early in hypoproteinia.*

It was the purpose of the present work to determine in patients ill with chronic pulmonary tuberculosis: (a) to what extent the protein nutrition was reflected by the factors involved in the nitrogen balance; (b) the deviation from normal of the body fluid compartments, of the erythrocyte mass, and of plasma proteins; and (c) the effects of a high protein regimen on (a) and (b).

All the patients selected for this study were males ill with advanced chronic progressive tuberculosis. They had bad prognoses because of continuing fever, and loss of weight and strength.

PART I

The Caloric and Nitrogen Intake and Nitrogen Excretion

Materials and Methods

The food as routinely served in the tuberculosis wards was weighed before consumption,

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* *Hypoproteinia*, a term analogous to anoxia for systemic oxygen deficiency, is here used for systemic protein deficiency.[6]

TABLE I

Daily Routine Diet Record of Eleven Cases of Chronic Pulmonary Tuberculosis

Number	Initial wt.	Days studied	Caloric intake*				Nitrogen intake			Nitrogen output (mean values)			
			Highest	Lowest	Mean	Cal./KBW	Highest	Lowest	Mean	Urinary N	Fecal N	Sputum N	N bal.
	Kg.									*Gm.*	*Gm.*	*Gm.*	
1	'50.2	6	5070	2140	3010	60′	30.18	6.37	15.19	10.40	1.01	0.46	+4.32
2	'58.6	10	2310	1000	1310	29′	16.86	5.5	9.75	7.2	0.71	0.37	−1.47
3	'55.5	6	2680	2110	2330	42′	21.16	8.5	11.97	7.69	0.44	—	+3.84
4	45.5	5	1990	1200	1580	34′	10.59	6.02	7.31	6.9	0.66	—	−0.25
5	'48.	5	3380	1540	2210	46′	27.27	10.36	13.44	8.51	0.91	—	+4.02
6	'48.	5	1580	1000	1400	29′	15.04	5.7	7.59	6.75	1.86	1.15	−2.17
7	'51.4	6	2410	1830	2050	40′	16.16	8.76	10.76	7.39	1.12	0.56	+1.69
8	'54.1	10	2720	650	1250	35′	15.7	4.25	8.94	6.25	1.58	0.43	+0.68
9	'55.	10	2450	1020	1150	21′	14.2	6.16	7.96	7.6	1.4	0.41	−1.81
10	'53.9	6	2410	1320	1680	36′	14.88	7.17	9.9	5.43	3.19	0.43	+0.85
11	'51.8	5	1370	1150	1200	27′	20.	9.76	13.17	20.61	1.74	0.12	−9.3

* Figures rounded to nearest 10.

and the plate wastage was reweighed after the patient had eaten. The caloric and protein values of the part consumed were calculated from a table of food values.[7] These studies lasted from *five* to *ten* days. The methods used for measuring urinary, fecal, and sputum nitrogen have been described elsewhere in a previous communication.[8]

The Caloric and Nitrogen Intakes

The data recorded in Table I show that both caloric and nitrogen intakes fluctuated widely from patient to patient and from day to day. The maximum caloric intakes appeared nutritionally ample, but the mean level intakes were satisfactory in only four patients, while in only seven were the minimal values above 25 calories per kilogram body weight (cal./Kg.). The nitrogen intake also fluctuated, ranging from a high of 30.18 Gm. to a low of 4.25 Gm. per day.

The fluctuations in caloric intake were wider than those observed by Brewer *et al.*[9] and by McCann.[3] Brewer *et al.* studied thirty women with active pulmonary tuberculosis and found that caloric intakes ranged from 1300 to 3000 calories per day. The design of the McCann study differed from ours. He stimulated dietary intake "by special cooking, in order to make it possible for the patients to ingest the required amount," and planned his study to determine the level of feeding at which nitrogen equilibrium could be maintained.

The nitrogen intake of our patients, although often low, did not sink to the level found by us in patients with gastrointestinal cancer.[10] Presumably the data reflect the change in appetite as affected by the evolution of tuberculosis and of cancer of the gastrointestinal tract.

Urinary Nitrogen

The nitrogenous substances found in the urine may be divided into those of metabolic and those of non-metabolic origin. The latter are exemplified by proteinuria, hematuria, local exudation, or desquamation of tissues of the urinary tract. One factor leading to increased metabolic azoturia in disease is inadequate caloric intake. A second factor is the so-called "catabolic response" to damage, perhaps associated in some way with the "alarm reaction." This was formerly thought to be due to the protein catabolic effect of an increased production of adrenoglucocorticoid hormones in response to the "stress" of disease, but Engle[11] has indicated that these hormones are not the primary cause of azoturia following stress. The azoturic response, which is pronounced in the early days of diseases afflicting normal well-nourished subjects, may be absent in hypoproteinia.

The level of daily total urinary metabolic nitrogen varies with protein intake. Lusk[12] found it not to be in excess of 12 Gm. for medical students in the New York area, while the

average value of Keys *et. al.*[5b] for the 32 subjects during the prestarvation period was 13.2 Gm. In our studies at Bellevue Hospital, values above 8.5 Gm. were rare during the control periods.[13] This low output reflects either a low protein diet, a chronic hypoproteinia, or both, in patients drawn from a low economic level in New York City.

An examination of the mean values in Table I reveals that all but one fell below 13.5 Gm., and in six patients (Nos. 3, 4, 6, 7, 9, and 10) were below 8.5 Gm. N per day.

These values do not suggest a strong catabolic response.

Fecal Nitrogen and Sputum Nitrogen

In 1944, Albright, Reifenstein, and Forbes,[14] on the basis of a study of the normal fecal nitrogen at 33 different levels of nitrogen intake, established criteria for standard values of fecal nitrogen. Comparison with these values showed that the mean fecal nitrogen in our series was in the normal range in six patients (Nos. 2, 3, 4, 6, 9, and 11), significantly lower in three (Nos. 1, 5, and 8), and distinctly higher in patient 10. It is interesting in this connection that patient 4, with normal values, had tuberculous enteritis, while patient 10, who had high fecal nitrogen excretion, had no clinical signs of any gastrointestinal complication. There may be several opposing factors involved, for example, hypoproteinia, on the one hand, and associated gastrointestinal disturbances, on the other.

In eight of the eleven patients, the sputum was collected for analysis. The nitrogen loss in the sputum in these cases was low, varying from 0.12 to 0.56 Gm. daily, except in patient 6 in whom the loss was 1.15 Gm. daily. These values match those found by May[1] some fifty years ago.

Nitrogen Balance

Only four patients (Nos. 1, 3, 5, and 7) were in significantly positive balance at caloric intakes of from 40 to 60 cal./Kg. and nitrogen intakes of from 10.76 to 15.19 Gm. Two were in slightly positive balance (Nos. 8 and 10) with caloric intakes of from 35 to 36 cal./Kg. and nitrogen intakes of from 5.43 to 6.25 Gm., and five (Nos. 2, 4, 6, 9, and 11) were in frankly negative balance with caloric intakes of 27 to 34 cal./Kg. and nitrogen intakes of from 6.75 to 9.76 Gm. McCann[3] found that in some patients with caloric intakes of from 1.7 to 2.4 times the basal energy requirements, from 37 to 44 Gm. of protein was enough to maintain nitrogen balance. Brewer *et al.*[9] found that the protein intake necessary for nitrogen equilibrium in tuberculous patients was little or no higher than for the healthy individual.

Our results appear to confirm McCann's and Brewer's work in one respect, namely, that the tuberculous patient does not require a higher nitrogen intake than normal subjects to achieve nitrogen equilibrium. On the contrary, with reduction of tissue mass in hypoproteinia, the protein and caloric requirement to achieve equilibrium would be lower than that of healthy subjects. The significance of this is discussed later.

The data suggest that the cause of hypoproteinia in chronic tuberculosis is not a catabolic reaction but a prolonged low food intake. The fact that some patients on the same ward diet took enough to maintain nitrogen balance indicates that the major factor in reducing this intake was perhaps an aberration in appetite. How the appetite is affected by disease merits further study.

The experience with isoniazid in this disease would seem to support the impression that disturbances in appetite play an important role in the associated hypoproteinia. Selikoff and Robitzek[15] observed that with improvement in the clinical condition following the administration of this drug there was a greatly improved appetite, resulting in large weight gains; however, this increased appetite tapers off after the weight curve reaches a certain level.

PART II

Body Compartments

Patients

Twelve patients were studied, eleven of whom were the subjects from Part I. Patient 12 was also selected on the same basis of

weight loss, progressive "downhill" course, and poor prognosis.

Methods

The body compartments and blood constituents determined were:

1. The plasma volume (PV) according to the method of Gregersen *et al.*[16]
2. The total plasma protein level (PP) according to the falling drop method of Barbour and Hamilton.[17]
3. The hematocrit (HCT).
4. The extracellular fluid space (SCN-S) as determined by the sodium thiocyanate method of Lavietes *et al.*[18]

The foregoing were arrived at by direct determinations. From them the following were computed:

1. The plasma volume per kilogram body weight (PV/K).
2. The blood volume (BV).
3. The blood volume per kilogram body weight (BV/K).
4. The total circulating plasma proteins (CPP).
5. The circulating plasma proteins per kilogram body weight (CPP/K).
6. The red cell mass (RCM).
7. The red cell mass per kilogram body weight (RCM/K).
8. The thiocyanate space per kilogram body weight (SCN-S/K).

The value of the above measurements, primary and derivative, are useful only if premorbid values are available for comparison. Unfortunately, the premorbid data were not available, and to calculate their probable values from the premorbid weight given in the history is hazardous, as the range of such "normal" weights may be as wide as 33 per cent.

In our experience with hypoproteinia,[10,19] we have found the relative or per kilogram values more useful than the absolute. In the present work, therefore, in assessing the protein status, the data we obtained will be used only to derive the per kilogram values.

In simple hypoproteinia, in the ambulant patient, the PV/K, the BV/K, the CPP/K, and the SCN-S/K are elevated.[19,20,21,5b]

The elevation of the PV/K and of the SCN-S/K point to a tendency to store water which may be manifested as edema. This tendency, however, is decreased by bedrest, as has been shown by Denz,[22] so that in the recumbent patient the PV/K may be subnormal. This hypovolemia has been called "chronic shock" by Clark *et al.*[23] It is probable that other factors, such as electrolyte intake and diuresis, also affect this tendency to water storage in hypoproteinia. In normal individuals, Lyons, Jacobson, and Avery[24] have shown that the ingestion of sodium either as bicarbonate or chloride promotes water storage, causing an increase in weight and a rise in the plasma volume. Grant and Reischman[25] have confirmed this and also found a rise in the SCN-S. Because of this marked lability of water storage, both abnormally high and abnormally low values are found—the former when the patients are up and about and the electrolyte intake is unrestricted, and the latter when they are in bed and the electrolytes are restricted.

The data acquired in this phase of our study appear in Table II. In the appraisal of these data, it must be recalled that all the patients were at complete bedrest.

The Relative (per kilogram) Plasma Volume (PV/K)

The table shows this value to be within normal limits in seven patients (Nos. 4, 5, 6, 7, 8, 10, and 12). In patient 1 it was just above the upper limits of normal, and in patients 2, 3, and 11 it was significantly high, while in patient 9 it was abnormally low—39 cc. In view of Denz' observation on the effect of bedrest,[22] it is surprising that almost half of these cases, all of whom were at bedrest, showed elevation of PV/K. As suggested above, other factors besides physical activity must play a part in determining the value of PV/K.

The Relative (per kilogram) Blood Volume (BV/K)

The total blood volume (BV) is derived from the plasma volume and the hematocrit, two factors which condition its value. The BV/K is derived from the total blood volume and

TABLE II

Fluid Compartments and Blood Constituents in 12 Cases of Chronic Pulmonary Tuberculosis

Case	Wt.	PV*	PV/W	PP	CPP	CPP/W	Hmt.	BV*	BV/W	RCM*	RCM/W	SCN-S*	SCN-S/W
	Kg.	*cc.*	*cc.*	*Gm. %*	*Gm.*	*Gm.*		*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*
1	50.2	2870	57	7.26	208	4.14	41	4860	97	1990	39.7	11500	229
2	58.6	4680	80	7.32	343	5.85	33.7	6960	119	2280	38.9	17600	300
3	55.5	3920	71	6.36	249	4.49	45	7120	128	3210	51.7	22220	400
4	52.3	2840	54	7.78	221	4.23	43*	4980	95	2140	40.9	16390	308
5	48	2240	47	7.85	176	3.66	49	4390	91.4	2150	44.7	16130	336
6	48	2260	47	7.78	176	3.67	47	4260	88.8	2000	41.7	17540	366
7	54.1	2370	44	7.53	178	3.29	40	3930	73	1560	28.8	16670	308
8	58.9	2570	44	6.74	173	2.94	38	4150	71	1580	26.9	22090	375
9	54.5	2130	39	7.5	160	2.97	45	3860	71	1740	31.8	19440	325
10	45.5	2160	48	6.73	145	3.19	40	3600	79.2	1440	32	16130	354
11	53.9	3680	68	5.6	206	3.82	35	5660	105	1980	36.8	22730	423
12	50.5	2640	52	6.74	178	3.5	48	5080	100.6	2440	48.2	11110	220
Mean			54.25	7.1		3.812	42.08		92.583		38.51		328.67
S. D.			12.01	0.681		2.904	4.72		17.56		7.32		58.9
Normal ranges			45–50	6.5–7.2		3.15–3.6	42–50		85–95		42–45.6		200–275

Wt. —Weight.
PV —Plasma volume.
PV/W —Relative (per kilogram) plasma volume.
PP —Plasma proteins.
CPP —Total circulating plasma proteins.
CPP/W—Total circulating plasma proteins (per kilogram) body weight.
Hmt. —Hematocrit.
BV —Blood volume.
BV/W —Relative (per kilogram) blood volume.
RCM —Total red cell mass.
RCM/W —Relative (per kilogram) red cell mass.
SCN-S —Sodium thiocyanate space.
SCN-S/W—Sodium thiocyanate space (per kilogram) body weight.
* Values rounded out to nearest 10.

the body weight in turn. If the normal values are set from 80 to 95 cc. per kilogram, the distribution of the data was as follows:

Five (Nos. 1, 2, 3, 11, and 12) abnormally high (relative hypervolemia).

Four (Nos. 4, 5, 6, and 10) normal limits.

Three (Nos. 7, 8, and 9) below normal (relative hypovolemia).

Since both abnormally high and abnormally low values may be expected in patients with hypoproteinia who are in bed, depending upon water retention, the last three cases may be included with the first five as being abnormal.

The Plasma Protein Level (PP)

Since it is by now generally known that the plasma protein level is not a reliable indicator of the protein status, the data on this phase of the study need not be discussed. Suffice it to say that only in patient No. 11 was there frank hypoproteinemia. Of greater interest is the occurrence of hyperproteinemia in six patients (Nos. 2, 4, 5, 6, 7, and 9). This may be due to an elevation of the gamma globulin, as found by Seibert, Adno, and Campbell,[26] or of both beta and gamma globulins, as reported by Volk, Saifer, Johnson, and Oreskes.[27]

The Hematocrit (HCT)

If the normal limits of this value be set between 42 and 50 in the male, the distribution of our cases is as follows:

Six (3, 4, 5, 6, 9, and 12) within normal limits.

Three (1, 7, and 16) borderline.

Three (2, 8, and 11) frankly subnormal.

Thus there was frank anemia in three subjects and probable anemia in three others. Since the body may lose 24 per cent of its weight without reducing the hematocrit below normal limits,[5c] this measurement is also unreliable. In addition, both the hematocrit and red count in pulmonary tuberculosis may be modified by hemoptysis.

The Relative (per kilogram) Red Cell Mass (RCM/K)

The RCM/K is derived from the hematocrit, the PV, and the body weight, and is normally from 42 to 45.6 cc. per kilogram of

body weight. Because this value is presumably less affected by hemodilution, it may be a better indicator of the red cell contents of the circulation than any of such relative indices as the red count and hematocrit. In the Minnesota series[5d] this value was initially 38 cc., dropping to 37 cc. and then rising again to 38 cc. after 12 and 24 weeks, respectively, of semistarvation. In our present series, of twelve such values two (7 and 8) were significantly subnormal, two (4 and 9) were just under the lower limit of normal, two (3 and 12) were significantly higher than normal, and six were within normal limits. As previously pointed out,[20] this entity is not a faithful indicator of the degree of hypoproteinia.

The Relative (per kilogram) Thiocyanate Space (SCN-S/K)

Taking 200–275 cc./Kg. as the normal range, there was significant elevation in ten of the twelve patients (all but patients 1 and 12), and in patients 3 and 10 it was over 400 cc. The lowest of these ten elevated values was in patient 2—300 cc. per Kg. When it is remembered that in the work of Grant and Reischman[25] the administration of from 20 to 30 Gm. of sodium chloride daily over a period of 3 to 4 days raised the SCN-S/K from an initial value of 180 cc. to nearly 250 cc./Kg., these high values acquire significance. It was stated previously[20] that in hypoproteinia the SCN-S/K in all probability does not measure faithfully the extracellular fluid space alone, and that some other factor, perhaps increased permeability of cell membranes to sodium thiocyanate, contributes to the enlargement of this value in hypoproteinia, both factors working in the same direction. In the absence of cardiac decompensation and of renal edema, and in the presence of weight loss, this elevation may be taken as an indication of hypoproteinia.

To summarize, patients 2, 3, and 10 had elevation of all four values—PV/K, BV/K, CPP/K, and SCN-S/K. Two had 3 abnormal values, patient 1 having elevated PV/K, BV/K, and CPP/K, while patient 4 had elevated BV/K, CPP/K, and SCN-S/K; four patients (5, 8, 9, and 12) had two abnormal values; while in only patient 11 was there one abnormal value, SCN-S/K. In none were all the four values entirely normal. The weight loss found clinically is then reflected in these presumptive stigmata of hypoproteinia—definitely in the first seven cases, and with probability in the last five.

The blood studies of Chortis[28] on 108 tuberculous patients with "hunger edema" furnish a valuable frame of reference. These blood studies "showed . . . a considerable decrease in the protein of the blood serum which in certain cases dropped to 1.4 per cent. A diminution of the total protein was noted, while the globulin remained at a normal level. Red blood cells were reduced to about 2 to 3 millions . . . while the hemoglobin was 55 to 75 per cent." Seventy-five cases had severe edema, 23 had diffuse edema, and 10 had slight edema.

In our study, hypoproteinemia was present in only one patient, while it was the rule in Chortis' patients. The erythrocyte count in Chortis' patients ranged from 2–3 million, i.e. 40 to 60 per cent of normal; our hematocrit values were reduced 73 to 76 per cent of normal) in only two patients (2 and 10), slightly abnormal in four, and normal in six. With regard to clinical edema, only patients 3 and 10 had over 400 cc./Kg. of extra-cellular fluid, with pitting edema of the ankles, while in most of Chortis' patients the edema was more marked.

PART III

The Effect of a High Protein Regimen

The first nine patients of this group were given an extraordinarily high protein regimen; the nitrogen balance, the clinical effects, and the changes in the fluid compartments and blood constituents were studied for the first 10 to 23 days, when protein deposition was most active. In patients 7, 8, and 9 the regimen was prolonged to 82, 96, and 113 days, but without further nitrogen balance study.

While the traditional "high protein diet" contains 120 Gm. of protein (19.2 Gm N or approximately 2 Gm./Kg.), in our study the nitrogen intake was raised from 100 to 400 per cent of that level. Two oral hydrolysate prep-

arations were used, although other forms of protein prepared in a finely divided state to facilitate absorption have subsequently been found to be more acceptable and to result in a lower incidence of diarrhea. The daily intakes were from 50–60 calories and 0.5 to 0.72 Gm. N/Kg., or 3.75 to 4.5 Gm./Kg. of protein. The subjects were also given a National Research Council-recommended[29] complement of vitamins; the mineral intake was assumed to be adequate.

The advantages and disadvantages, as well as the special conditions attending such a high protein regimen in hydrolyzed or finely comminuted form, have been discussed at some length in previous reports.[6,19,30] Briefly, there is less fullness and satiety than from a corresponding amount of conventional protein food, so that more frequent administration is possible, and consequently a higher total intake. In the presence of caloric, vitamin, and mineral adequacy, the administration of this regimen to hypoproteinic subjects results in high positive nitrogen balances, large weight gains, and speedier nutritional recovery—in from one-half to one-fifth of the time required when conventional dietetic regimens are used.

It has been postulated that the higher amino acid level in the intestine forces a rise in the level in the body fluids, which in turn causes a higher deposition of proteins than is otherwise possible. It must, however, be pointed out that this increased protein ingestion is accompanied by increased respiratory activity, reflecting the classical specific dynamic effect of proteins. The possible influence of this factor in tuberculosis will be discussed later.

Changes of Fluid Compartments and Blood Constituents in Simple Hypoproteinia during Protein Therapy

The changes occurring under high protein therapy in patients with simple hypoproteinia, i.e., without existing disease, have been discussed in a previous report.[19] They may be summarized briefly as follows:

As proteins are deposited, a preliminary weight loss is the rule, attributable to a rapid loss of extracellular fluid. The weight of this fluid loss overbalances the weight of tissue deposited. This loss lasts from 3 to 10 days and is promptly followed by a gain in weight which sometimes attains $^1/_2$ to $^3/_4$ kilograms daily for the first few days. Thereafter, the rise is steady until a plateau is reached. The nitrogen balance, immediately positive, may be as high as 30 Gm. a day. This high storage is most marked in the first week to ten days, tapering off subsequently. The plasma volume undergoes rapid expansion, reaching a peak in three to four weeks and gradually falling to normal. The hematocrit and red cell mass may show an initial fall, usually more pronounced than that of plasma proteins. After this lag, the rise, too, is rapid; it is steadier and suffers less from aberrations than the plasma protein curve. Both plasma protein concentration and total circulatory protein may be stationary or may even fall during the first few days. After this, the rise in both plasma protein concentration and total circulating protein, especially in the albumin moeity, occurs rapidly. The sodium thiocyanate space tends to fall at a uniform rate. The factors governing the speed of the fall have not been determined and presumably include the electrolyte metabolism and physical exertion.

The Nitrogen Balance and Weight Data

A detailed record of the nitrogen balance record of patient 9, representative of all nine patients, appears in Table IV. The nitrogen balance was highly positive from the first period on. In the other eight patients, whose balance data appear in abbreviated form in Table III, the nitrogen deposition averaged 6.98 to 18.24 Gm. daily. This high protein deposition simulates that found in cases of other chronic illnesses, as reported by Waife, Wohl, and Reinhold,[31] and is in general agreement with their schema of protein repletion following increased intake in poorly nourished subjects.

Patient 9 on the third day of the study, when the nitrogen retention was 74.1 Gm. for the first three-day period, lost 1.3 Kg. This weight was completely regained by the 14th day, and by the 21st day was 4Kg. above initial weight.

TABLE III

Patient 9

Nitrogen Balance Record under Hyperproteinization with Protein Hydrolysate (Nitrogen Values in Grams)

Date 1945	Wt.	N—intake Food N	Hydr. N	Total N	N/KBW	N—output Urin. N	Fecal N*	Total N	Total N retained (3-day periods)
	Kg.				*per day*				*Gm.*
3/27′	54.55′		36′						
28			36	108	0.50	29.18	4.74	33.92	74.09
29	53.18		36						
30			36						
31			36	108	0.50	44.43	4.74	49.17	58.83
4/1			36						
2	54.32		36						
3			36	108	0.50	63.64	4.74	67.38	49.17
4			36						
5			36						
6		3.84	36	111.84	0.50	96.77	4.74	101.51	10.13
7			36						
8			36						
9	55.11	16.96	39	133.96	0.55	59.25	4.74	63.99	69.97
10			42						
11	56		42						
12		37.6	42	162.60	0.55	106.97	4.74	111.71	50.89
13	57.04		42						
14			42						
15		31.68	42	157.68	0.60	78.53	4.74	83.27	74.41
16	58.52		42						
17			42						
18		29.12	42	113.12	0.55	77.89	3.16	81.05	32.07

* Mean of pooled values of first 7 periods.

Similar preliminary losses and subsequent gains were shown by patients 2, 3, 7, and 8. Patient 1, whose nitrogen retention and changes in body compartments were quantitatively less than in other patients, had no preliminary weight loss and gained only 1.7 Kg. in 22 days, data suggesting only mild hypoproteinia.

Under prolonged high protein therapy (Table IV), patient 7 had gained 12.1 Kg. by the 89th day; patient 8 had gained 8.5, 14, and 17.2 Kg., respectively, by the 42nd, 76th, and 96th days; and patient 9 had gained 7.0, 10.8, and 12.5 Kg., respectively, by the 41st, 57th, and 113th days. Since the body weight is influenced by the amount of body water, these weight changes should be correlated with the fluid compartment changes and preferably with changes in total body water—which, unfortunately was not determined. It is to be noted that the weight gains of patients 7, 8, and 9 are apparently more dramatic than those of the patients of Selikoff and Robitzek.[15]

Plasma and Blood Volume Changes

As compared with patients with simple hypoproteinia, the plasma and blood volume changes following high protein therapy in hypoproteinic tuberculous patients are much less consistent, with a tendency to expansion in some and contraction in others. In the three prolonged cases, however, there is a late but signicant expansion in the blood volume. The inconsistent trends observed during the early period of protein therapy, are similar to those noted in cases of cancer.

The Plasma Protein Level (PP) and the Total Circulating Plasma Protein (CPP)

Except for patients 8 and 9, there was a consistent fall in these determinations during

TABLE IV

Changes in Fluid Compartments and Blood Constituents during Hyperproteinization in Cases of Chronic Pulmonary Tuberculosis

No.	Wt.	Days studied	Daily N intake	PV*	PV/W	BV*	BV/W	PP	CPP	Hem.	TRCM*	SCN-S*	SCN-S/W	Av. daily N retained
	Kg.		*Gm. per Kg.*	*cc.*	*cc.*	*cc.*	*cc.*	*Gm. %*	*Gm.*		*cc.*	*cc.*	*cc.*	*Gm.*
1	50.2	0	0.69	2870	57	4860	97	7.26	208	41	1990	11490	229	6.98 for 10 days
	51.9	22nd		3100	60	4690	90	6.73	208	34	1590	12200	235	
2	58.6	0	0.62	4680	80	6960	119	7.32	343	33.7	2280	17590	300	14.75 for 10 days
	61.4	14th		5050	82	7430	121	6.7	339	32	2380	15640	255	
3	55.5	0	0.64	3920	71	7120	128	6.33	249	45	3210	22220	400	17.88 for 10 days
	58.2	15th		3250	56	5340	92	6.17	201	39	2080	18180	312	
4	52.3	0		2840	54	4980	95	7.78	221	43	2140	16390	313	16.25 for 13 days
	54	17th		2910	54	5290	98	5.72	184	45	2380	16670	309	
5	48	0	0.5	2240	47	4390	91	7.85	176	49	2150	16130	336	11.47 for 10 days
	50	15th		2290	46	4080	82	6.24	143	44	1800	15630	313	
6	48	0	0.67	2260	47	4260	89	7.78	176	47	2000	17540	365	17.78 for 13 days
	50.3	7th		2350	47	4310	86	6.21	146	46	1960	16960	337	
	51.82	14th		2520	49	4420	85	5.92	149	43	1900	14180	274	
7	54.1	0	0.59	2370	44	3930	73	7.53	178	40	1560	16670	308	13.53 for first 17 days
	55	8th		2600	47	4170	76	6.75	175	36	1570	17990	327	
	57	15th		2590	45	4210	74	6.50	168	37	1560	19190	337	
	58.5	22nd		2520	43	4140	71	7.06	177	39	1530	20000	342	
	66.1	89th		2750	42	4570	69	6.1	168	40	1830	13810	209	
8	58.9	0	0.72	2570	44	4150	70	6.74	173	38	1580			18.24 for first 23 days
	60	12th		2560	43	4290	72	6.96	178	41	1760			
	63.6	26th		2330	37	4150	65	7.38	172	43	1780			
	67.4	42nd		2380	35	4400	65	7.65	179	46	2020			
	72.9	76th		2490	34	4720	65	7.62	186	45	2130			
	76.1	96th		2770	36	5200	68	6.94	202	47	2440			
9	54.5	0	0.8	2130	39	3860	71	7.48	159	44	1700			18.24 for first 23 days
	56	15th		2090	37	3780	68	8.08	168	47	1770			
	59.5	27th		2000	34	4400	74	8.34	199	51	2240			
	61.5	41st		2150	35	4250	69	7.07	151	48	2140			
	65.3	57th		2360	36	4760	73	6.25	147	47	2240			
	67	113th		2230	33	4370	65	6.7	149	49	2140			

* Values rounded to nearest 10.

the early period of protein therapy. This agrees with the response manifested by patients with simple hypoproteinia. The total circulating protein, however, either remained practically stationary or fell, unlike the response in patients with simple hypoproteinia. In the three patients on prolonged protein therapy the plasma proteins showed no tendency to rise, simulating findings in our cancer patients and those studied by Waife, Wohl, and Reinhold,[31] and suggesting a disturbance in the mechanism involved in plasma protein production.

The Hematocrit (HCT) and Total Red Cell Mass (RCM)

The HCT fell significantly in five patients and rose significantly in three, and slightly in two patients during the first 7 to 14 days during the early part of the regimen. The red cell mass fell markedly in two subjects, slightly in three, but rose in three. In the three protracted cases, however, a tendency to rise was seen in all. Thus the tendency to anemia in this disease may have a partly nutritional basis and may not necessarily be uncorrectable. The bizarre behavior of the red cell mass—falling in some cases and rising in others during this acute period of high protein deposition—may be explained by differences in the severity of the disease, which is known to exert an unfavorable effect on hematopoiesis. As reported elsewhere, an early fall in both hematocrit and red cell mass is also seen in cases of cancer[10] under high protein therapy.

The Thiocyanate Space (SCN-S)

The wide variability in the thiocyanate space

determined at various times during this study can be seen in the data shown in Table IV*.

Clinical Response

In all of these patients, the large positive nitrogen balance and the changes in the weight curve were accompanied by a prompt increase in strength and improvement in morale. This is in line with the experience with high protein therapy in hypoproteinia associated with other clinical conditions. While the local pulmonary lesions showed no appreciable radiological improvement after one to three months of protein therapy, neither did they show any advance. In a group of patients selected for such a study because of poor prognosis, this may constitute a real gain. The possibility also exists that longer periods of high protein therapy might bring about an improvement in the lesions. This raises the question as to what part of the improvement following isoniazid therapy is attributable to nutritional improvement *per se* and what part to drug action.

Discussion

Historically, the dietetic management of pulmonary tuberculosis has undergone two phases. In the first phase, a diet rich in "eggs and milk," i.e., a rich diet or one with high protein content, was encouraged, and is still recommended in texts on clinical nutrition.[32,33] The most prominent exponents of really high protein feeding are the Pottengers,[34] who use as high a level as 250 Gm. of protein daily with reportedly favorable results.

However, the question of high protein feeding has been questioned by McCann[3] because of increased respiratory activity resulting from the specific dynamic action of protein. This concept has apparently had an effect on the current management of the disease, since in two recent texts on tuberculosis the protein factor was ignored entirely in one[35] and mentioned only casually in the other.[36]

Actually, McCann's work has been misinterpreted. Thus, the title of his paper was "The Protein Requirements in Tuberculosis," when it would have been more accurately entitled "Protein Requirements for Nitrogen Equilibrium in Tuberculosis."

This identification of protein requirements for nitrogen equilibrium with the protein requirements of the body in health may be justifiable in the normal individual where only maintenance is required. When applied to a hypoproteinic subject who needs *more* than the maintenance level for replenishment of protein loss and for recovery, this identification can be harmful.

With each day's loss of protein and further reduction of tissue mass, a lower and lower protein and caloric intake is required to attain equilibrium, so that an equilibrium reached at a low plane of intake is more an indication of hypoproteinia than of normoproteinia. In fact, the ease of attaining equilibrium has been suggested as a means of detecting hypoproteinia. Under these circumstances, to give proteins in the amount required *only* for nitrogen equilibrium would keep the state of hypoproteinia *in statu quo*.

The level of protein intake of 69 to 90 Gm. recommended by McCann for the tuberculous patient is more than sufficient to promote mere positive equilibrium in most patients. However, if hypoproteinia is present, the degree of positivity so attained is inadequate in the light of recent nutritional thought. The nitrogen retention scored by his best case at a protein intake of from 89.5 to 96 Gm. of protein over a period of nine days, averaged only 4.3 Gm. per day. Allowing one gram for nitrogen lost in the shed skin, hair, and nails, only 3.3 Gm. of protein would be available for healing and for repletion of lost proteins provided any had occurred. In a person who has lost 29 Kg. of tissue, it would take this small amount of consistently retained nitrogen at least 200 days to replace the loss.

Nor can the use of calorigenic foods in an attempt to spare proteins be too heavily depended upon, since even the maximum sparing action will be futile if there is little or no protein to spare.

* Unfortunately, the value of the SCN-S on the third day subsequent to an initial determination was not obtained because it was felt that the still high level of the thiocyanate in the blood at this time might vitiate the value of the second test.

On the other hand, Pottenger's level of 250 Gm. may not be necessary in patients who are not or are only slightly hypoproteinic, and an ingestion of that amount may, by stimulating respiratory activity, retard the process of recovery to that extent. Thus it would appear that to prescribe a preset and static level of protein intake, without regard to the presence or absence of hypoproteinia, is unjustifiably arbitrary.

That protein feeding is attended by "specific dynamic action," of which one manifestation is increased respiratory action, is not an academic problem, particularly at a high level of intake. Co Tui and Garcia[37] found that oxygen consumption can be raised by from 25 to nearly 100 per cent in one hour following the ingestion of protein hydrolysates in the amount of 0.09/Kg. of nitrogen and from 20 to nearly 60 per cent with an equivalent quantity of beef proteins.*

The question raised here is: Which is more harmful—hypoproteinia, which jeopardizes healing because of shortage of healing material, or rapid protein replacement, which favors healing but stimulates respiratory activity? It would appear that the solution to this question is to be found only in controlled investigation. In our three patients under prolonged high protein therapy with protein hydrolysate the disease showed no worsening.

Along these lines, studies with isoniazid should attempt to answer two questions: (1) whether the increased food ingestion resulting from the increased appetite stimulates respiratory activity, and to what extent this may be harmful; and (2) whether the increased appetite is being fully utilized to insure the most rapid replenishment. The fact that in the published weight curves of Selikoff and Robitzek[15] the preliminary dips are more prolonged and the weight gains less than in our patients 7, 8, and 9, perhaps indicates that full advantage is not being taken of this "insatiable" appetite reportedly stimulated by the drug.

* Other factors aside, this finding would make whole proteins theoretically safer to use in tuberculosis than protein hydrolysates.

Summary

Nitrogen equilibrium studies in a limited number of patients suffering from advanced chronic pulmonary tuberculosis with weight loss and a poor prognosis showed that there is, as a rule, no increased azoturia, so that the weight loss is not due to a "catabolic response" or "toxic" destruction of proteins. The weight loss is probably caused by disturbance of the appetite and is reflected by the presence of one or more changes in the body fluid compartments associated with hypoproteinia.

The use of high protein therapy is followed by a highly positive nitrogen balance and rapid weight gains; there does not seem to be an antianabolic factor in the disease.

The adverse effect on erythropoiesis and blood protein formation in pulmonary tuberculosis does not appear to be due to hypoproteinia alone; but the disease itself seems to play a role.

The effect of rapid protein replacement on increased respiratory activity associated with the specific dynamic action of high protein ingestion is discussed.

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RESUMEN

El estado proteico en la tuberculosis pulmonar

Estudios del equilibrio nitrogenado en un número limitado de casos avanzados de tuberculosis pulmonar crónica, con pérdida de peso y grave prognosis, demostraron que no hay, generalmente, ningún aumento de azoturia y, por consiguiente, que la pérdida de peso no representa una "respuesta catabólica" ni una destrucción "tóxica" de proteínas. La pérdida

de peso resulta con probabilidad de un disturbio del apetito, y se refleja en una o más alteraciones en los espacios flúidos del cuerpo, en asociación con la hipoproteínia.

El empleo de la terapia proteica masiva logra un equilibrio nitrogenado marcadamente positivo y un rápido aumento del peso corporal; no parece exista un factor anti-anabólico en la enfermedad misma.

El efecto adverso sobre la eritropoyesis y la formación de proteínas sanguíneas en la tuberculosis pulmonar no parece sea debido a la sola hipoproteínia, sino a la enfermedad misma.

Se discute el efecto de la administración rápida de las proteínas sobre el aumento de la actividad respiratoria, en relación con la acción dinámica específica de una dieta rica en proteínas.

The Prehistory of Eating

"While foods and feeding habits of earliest man have been equated with those of large modern apes, mainly from the character of fossil teeth, the evidence points clearly to an omnivorous diet. . . . It is a fact that primal man ate many lowly foods both from necessity and choice and his self-selection was sound. . . . 'Nut-eating' men, as the Ancient Greeks viewed savage outlanders, were well supplied with thiamin, riboflavin, niacin, and vitamins A and C in some nuts. Primal man in all epochs ate to repletion when food was abundant. When food was scarce, he tightened his waistband, if he wore one, and starved philosophically. . . . Modern man often tightens his belt or waistband by overeating."
—L. B. Jensen. *Man's Foods,* The Garrard Press, Champaign, Ill., p. 2.

Progress: Woman's Work

"Practically all of the inventions and devices of early food-producing times, pottery, sickles, rubbing-querns, planting-sticks, baking, fermentation of beer and bread, planting, cultivating, reaping and storing of grains, and spinning flax were the work of women. The Neolithic Revolution, leading to civilization as we know it, can be accredited to Woman, who was also the first botanist. Whether or not she tried out a new plant for its edibility on her lord and master is not known, but brewing she did, and stimulated the representatives of the early gods, until by 3000 B.C. intoxicants were necessities for sage and serf, king, general, and tax collector. The millennium preceding 3000 B.C. produced more useful and important discoveries than any period until the Renaissance and the Colonial expansion period of Europe."
—L. B. Jensen. *Man's Foods,* The Garrard Press, Champaign, Ill., 1953, pp. 50–51.

Cannibalism

"It is a melancholy fact to record that all races from the beginning to present have been cannibals. The practice existed for a variety of reasons: hunger and famine, ridding tribes of useless members, prisoners of war, and absorbing virtues of the brave. . .

"There have been modern apologists, notably M. Roberts (1920), and A. H. Keane (1920), who state in sequence, 'Cannibalism has been a powerful factor of progress and human advance.' 'Here again in Africa the observation has been made that tribes most addicted to the practice also excel in mental qualities and physical energies, nor are they strangers to the finer feelings of human nature!'

"There is a large literature on this grisly subject, but suffice it to say that the only scientific virtue that comes to mind is that such 'food' will not incite allergy, since homologous proteins are not antigenic for the same species."
—L. B. Jensen. *Man's Foods,* The Garrard Press, Champaign, Ill., 1953, p. 19.

Does a LOW *Intake of* CALCIUM *Retard* GROWTH *or Conduce to* STUNTEDNESS?

By A. R. P. WALKER, M.SC., PH.D.*

IT IS ALMOST universally accepted that the level of calcium intake of the young influences their rate of attainment of height. According to Sherman,[1] steady growth in children requires a high intake of the element. Concerning low intakes, Venar and Todd[2] and, more recently, Stearns,[3] maintain that there is ample evidence that deficient intake or utilisation of calcium and other mineral salts result in slowing down growth and lengthening of growing period. Several authorities, moreover, go further and take the view that a low intake of calcium conduces to stuntedness.[4-10] In tropical and semitropical countries, low calcium intakes are usual, and the calcium-phosphorus ratio occasionally is as wide as 1:10. The retarding effect on growth would therefore be expected to be well marked, and in this connection, McCance and Widdowson[11] have referred to the smallness of the children from such parts, linking up this characteristic with the prevailing "sub-optimum level of calcium nutrition." Despite the general acceptance of this particular role of calcium, and the assurance with which the belief is often stated, no one appears to have investigated its validity.

Growth, of course, requires other dietary components in addition to calcium. Furthermore, growth is influenced certainly by hereditary, and possibly other factors.[12] Hence, where retardation is demonstrable, it could be due, not only to a low intake of calcium, but to the operation of other single or multiple dietary or non-dietary factors. Ideally, to supply an unequivocal answer to this question of the role of calcium intake in growth, it would be necessary to have a single homogenous population among whom comparable age groups differed only by one factor, i.e., level of calcium intake. The more two groups differ from this situation, due to the presence of other variables, the greater will be the uncertainty of the validity of the conclusions drawn. Needless to say, this ideal state is never observed, for neither homogenous population groups nor diets of widely varying calcium content though otherwise nutritionally adequate are encountered in practical human nutrition. At the outset, therefore, it will be apparent that it is highly improbable that a clear answer can be given as to whether level of calcium intake is or is not of critical importance in the attainment of height.

It is now proposed to illustrate and amplify the difficulties described by referring firstly, to the height of children of the same age; next,

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to height of adults at maturity; and lastly, to studies bearing on the use of calcium supplements under controlled conditions.

The Height of Children of the Same Age

Several authorities in different parts of the world, for example, Orr[13] in Great Britain, Nicholls and Nimalasuriya[14] in Ceylon, and le Riche[15] in South Africa, have shown that children from poor families are less tall than children of the same age from better class homes. Differences in the diet consumed, especially in regard to calcium intake, are usually considered to bear chief responsibility.[3,7,16,17] However, as far as one is aware, no critical evidence has yet been adduced to show that the low calcium intake of the less tall sections is *specifically* implicated in retarding growth.

There is no dispute that Western children are taller than indigenous children of the same age groups dwelling in tropical and semitropical regions. This general observation has been made by Stearns,[8] and considerable supporting evidence is available, for example, the recent investigation of MacKay and Martin[18] on a tribe of Kenya Bantu. Yet the phenomenon is not invariably observed, for in the study of Welbourn,[19] it was reported that the mean height of the Kampala Africans examined at 8 years was greater than that of local European children of the same age group and, incidentally, coming from very good homes. It must be appreciated that the value of any relevant information on non-White groups is limited because (1) their ages are known with far less certainty than is the case with Western children; (2) little knowledge is available on their periods of growth spurts, whether they coincide or not with those of Western children; and (3) it is not known whether the increases in height of children of all classes which have occurred in Europe, North America, India, and Japan have yet affected the African races.[20] But quite apart from these uncertainties, there appears to be no evidence that the low calcium intake of the child populations of tropical and semitropical countries is specifically involved in retarding their rate of attainment of height.

Height at Maturity

When one considers final height, the uncertainties referred to fall away. Orr[21] has pointed out the strong body of opinion which considers that adult height is not correlated with nutrition, and that stature and configuration of body are inherited and cannot, to any significant extent, be affected by diet. Temporary retardations may occur as in wartime or in famine, but the growth urge is believed to be so strong that the ultimate predestined stature is attained on any ordinary diet. There is much evidence that with growing children, temporary dietary restrictions do, in fact, become nullified in time after resumption of the previous habitual diet. This was observed, for example, with the German children of World War I,[22] also with the French children in the last war.[23] On the other hand, the observations of Shapiro[24] on the physical characteristics of Japanese immigrants and their offspring in Hawaii are pertinent; he found an average difference of 4.1 and 1.7 cm. in the height of adult males and females, respectively, in favour of Hawaiian born, which showed that heredity is not the only factor determining stature at maturity. The different observations cited merely underline the complexity of the subject by indicating the almost insuperable difficulties inherent in efforts to assess the relative importance of the individual influencing factors.

Nevertheless, it would seem reasonable to suggest that if the level of calcium intake is a *critical factor* in the attainment of height, then low consumers of the element should be invariably stunted. But what is understood by being stunted? By how many inches must a population group be shorter than a better fed Western population group before the former may be labeled as stunted? McLester and Darby[25] have defined *leanness* as a condition of the body in which weight is 15 per cent or more below normal. Were the same proportion valid for height, then taking 6 ft. as an arbitrary height, a person would have to be less than 5 ft. 1 in. before being described as undersized or stunted. Using this reckoning, only certain groups of pygmies could be put into

TABLE I

The Height of Population Groups at Maturity

Observer	Population group	No. examined	Height
Turner[26] (1910)	South African Bantu		
	East Coast Bantu	1337	66.5 in.
	Transvaal Basuto	521	66.0 in.
	Cape Province Bantu	680	66.25 in.
Walker[27] (1954)	East Coast Bantu	1100	66.35 in.
	Transvaal Basuto	650	66.25 in.
	Cape Province Bantu	720	66.1 in.
Carlson[28]	United States Army recruits	800,000	67.5 in.
Clements and Pickett[29]	Scotsmen, National Service recruits	1303	66.82 in.

the latter category. As far as I am aware, no precise figure has yet been advanced to define stuntedness. However, to illustrate that low calcium consumers are certainly not all stunted at maturity, Table I has been compiled, in which data on three South African groups are given, also two Western groups.

The South African Bantu groups were composed of mine-labourers who were measured at the Witwatersrand Native Labour Association Headquarters in Johannesburg, the clearing centre through which pass over a quarter of a million workers annually. The groups were selective only in so far as there is no compulsion to work on the Mines. But the tribal social status of the individual is so enhanced, and, moreover, the remuneration accruing is so apt a way of saving money to buy cattle for the acquiring of wives (the *lobolo* system), that only serious disability prevents volunteering for service. The differences between the two sets of Bantu data are not significant; furthermore, the latter data[27] refer only to *new* adult recruits, thereby obviating the effects of the excellent diet provided by the Mines. The data on the American and British adult males refer to unselected subjects.

The mean heights of the South African Bantu males from the regions mentioned in all cases are less (roughly 1 and 2 per cent respectively) than the mean values given for the two groups of White subjects. But the inferiority is surely insufficient to label the former people as stunted, despite habituation to a low calcium diet, i.e., 200–450 mg. *per diem*.[30–35] While it is probable that the more plenteous sunlight enjoyed by dwellers in tropical and semitropical countries compensates in part for their low intake of calcium, the fact remains that the latter handicap apparently has not markedly prejudiced the height of the adult Bantu groups cited.

There is, however, one Bantu group whose intake of calcium is relatively high. In Nyasaland, Barker[36,37] reported that potashes (plant ashes) are included in the customary diet almost every other day. The ashes of similar plants found in the Union contain approximately 2–5 per cent of calcium.[38] According to Barker (*loc cit*), an adult may ingest an average of 2 oz. ashes *per diem*, this amount contributing a supplement of over a gram of inorganic calcium. While it would be imprudent to lay stress on the accuracy of these figures, there is no doubt that the Nyasaland Bantu with his supplement of calcium salts ingests a larger amount of the element compared with the South African Bantu, many regional groups of whom do not use potashes. At the Witwatersrand Native Labour Association Headquarters, previously referred to, the height of 480 consecutive Nyasaland adult male new recruits was found to average 65.7 in., a figure slightly less (though not significantly so) than the data for the Bantu groups given in Table I. The important point would seem to be that the probably large difference in the calcium intake of these Bantu populations has not promoted a marked difference in height at maturity.

The Effect of Calcium Supplements on Height Increments

In seeking more information concerning the question at issue, a further avenue of approach is to examine evidence bearing on the use of calcium supplements under controlled conditions. The following investigations are thus of interest: the first, on African boys, and the second, on Indian children.

In Kenya, at Kabete Reformatory, Orr and Gilks[39] investigated the effect of various dietary supplements on the growth of African

boys, of ages 10–17 years, engaged on farm work. Each of the four groups of 40 boys received one of the following diets. (1) The basal diet was composed of maize, beans, potatoes, ghee, and salt; it provided 3270 calories, 112 Gm. protein, and *560 mg. calcium* per diem. (2) The second group received the basal diet plus $^3/_4$ lb. maize, providing in all, about *620 mg. calcium*. (3) The third group consumed the basal diet plus $^1/_4$ lb. maize, which included 2 Gm. bone flour—providing in all about *980 mg. calcium*. (4) The fourth group received the basal diet plus 1 pint skimmed milk—providing in all about *1250 mg. calcium*. The experiment lasted for six months, although the measurements, etc., were continued for a further six months. The results obtained were as follows:

TABLE II

The Effect of Various Food Supplements on Height Increments

Diet	Supplement period. Average increase in height after 6 months	No supplement period. Average increase in height after 6 months
(1) Basal diet (560 mg. calcium)	0.71 in.	0.66 in.
(2) Basal diet plus maize (620 mg. calcium)	0.97 in.	0.79 in.
(3) Basal diet plus maize and bone flour (980 mg. calcium)	0.94 in.	0.76 in.
(4) Basal diet plus skim milk (1250 mg. calcium)	0.99 in.	0.76 in.

The calcium present in the bone flour is known to be available for absorption and metabolism.[40] If the height of the boys was being specifically retarded by lack of calcium, the height increments in groups (3) and (4) would be expected to be greater than in group (2). This was not the case. Within its experimental limitations, the investigation does not indicate that the low calcium intake in group (2), which amounted to about half the recommended allowance, was prejudicial to the rate of growth of the boys. Orr and Gilks[39] suggested that the additional increments in height in the supplemented groups were probably due to the extra calories supplied.

In an investigation carried out in India, Aykroyd and Krishnan[41] gave 36 children, of ages 3 to 6 years, a daily supplement of 65 mg. calcium (as lactate) for a period of 4 to 5 months. The children, in poor nutritional condition, and habituated to an unspecified but presumably small amount of calcium, gained more rapidly in weight and height than did 40 similar subjects not receiving the supplement. Later,[42] in 1939, these workers reported that when a group of 46 poorly nourished Indian children, of ages 6 to 12 years, were given a daily supplement of 130 mg. calcium (as lactate) for 11 weeks, they also made significant gains over 44 controls in both weight and height. The results of the two investigations are summarised in Table III.

TABLE III

Increases in Height of Indian Children with and without Calcium Lactate Supplements

Age	Period	Average increases in height	
		Calcium lactate group	Control group
3–6 years	4–5 months	0.63 in.	0.42 in.
6–12 years	11 weeks	0.86 in.	0.72 in.

The conclusion that the increased height increment was due *specifically* to a previous deficiency of calcium seems self-evident. Nevertheless, there are two points which argue against its ready acceptance. Firstly, the calcium lactate groups gained weight more rapidly than did the control groups, indicating that the supplemented groups consumed more food. The responsibility for the additional increase in height may thus have been shared between the calcium lactate supplement and the additional food eaten; to ascribe it wholly to the former is unwarranted. Secondly, it is well known that many compounds stimulate the appetite, directly or indirectly, but such an effect surely need not arise from their previous deficiency. Thus, the spectacular acceleration in growth produced in various animals by antibiotics (recently reviewed by Braude *et al*).,[43] cannot be attributed to a previous dietary deficiency of these substances.

From the experiments described, therefore, it cannot be assumed with certainty (1) that the acceleration of growth arose from calcium supplementation *per se:* (2) that a previous deficiency of calcium prevailed; and (3) that calcium was the only key which fitted the metabolic lock and released or promoted the additional increases in heights.

Discussion

It must be reiterated that the sole point at issue in this paper is whether population groups or races ingesting an amount of calcium *per diem* considerably less than the recommended allowance, are specifically stigmatised by retarded attainment of height, and by stuntedness at maturity. From what has been discussed, and as far as one can tell from the large volume of other relevant information, there appears to be no evidence that differences in the height of children or of adults are influenced by differences in calcium intake. It is, of course, well known that restriction of calcium intake in an otherwise adequate diet when fed to growing rats, *does* cause retardation of skeletal development.[44] There is little information available, however, on the low level where such retardation becomes operative in man. Apart from gross undernutrition, as in famine conditions, it is submitted that the critical level lies *below* the wide range of calcium contents of everyday diets consumed in different parts of the world.

Summary

It is widely accepted that in humans a low intake of calcium prejudices the rate of attainment of height and makes for ultimate stuntedness. There are, however, so many factors, dietary and non-dietary, which influence growth, that a precise assessment of the particular role of calcium is well nigh impossible.

Children from poor homes, and probably with a relatively low calcium intake, are certainly inferior in height compared with better class children of the same race and country. In addition, usually, though not invariably, indigenous children from tropical and semitropical countries, habituated to a low intake of calcium, are inferior in height compared with Western children. In neither case, however, is there evidence that differences in calcium intake are specifically implicated.

Where calcium supplements have been fed for short periods to children and youths accustomed to intakes of calcium less than the recommended allowances, there appears to be no critical evidence that these additions have specifically produced increments in height beyond such observed in controls.

The conclusion is reached that it has not been established that calcium intake *per se* is of importance in regulating height. It is suggested that apart from gross undernutrition, the critical intake of calcium below which retardation of growth occurs, lies *below* the wide range of calcium contents of everyday diets consumed in different parts of the world.

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Resumen

¿ Conduce un consumo escaso de calcio a un retraso del desarrollo y crecimiento insuficiente?

Es comunmente aceptado que un consumo escaso de calcio perjudica, en el hombre, a la velocidad del desarrollo de la estatura y conduce finalmente al crecimiento insuficiente. Hay, sin embargo, tantos factores, así dietéticos como no dietéticos, que influyen sobre el crecimiento, que resulta casi imposible determinar con exactitud el papel del calcio.

Los niños de hogares pobres con un consumo probablemente insuficiente de calcio son ciertamente de estatura inferior, en comparación con niños más afortunados de la misma raza y del mismo país. Es, ademas, un hecho común, si no invariable, que los niños indígenos de países tropicales o semitropicales, habituados a un consumo escaso de calcio, sean de estatura inferior, comparados con niños occidentales. En ningún caso, sin embargo, hay evidencia de que diferencias en el consumo de calcio sean específicamente implicados en este retraso del desarrollo.

Ahí donde suplementos de calcio se han suministrado durante cortos períodos a niños y jóvenes acostumbrados a consumir cantidades de calcio menores que las recomendadas, no parece exista evidencia de que estas adiciones, específicamente, hayan producido incrementos de estatura mayores que los observados en sujetos de control.

Se concluye que no queda establecido que el consumo de calcio sea, por sí solo, de importancia en la regulación de la estatura. Se sugiere que, aparte de la hiponutrición manifiesta, el nivel crítico de calcio en la dieta, por debajo de la cual ocurre una retardación del crecimiento, se halla *por debajo* de los límites anchos del contenido de calcio de las dietas ingeridas diariamente en varias regiones del mundo.

The Slow Triumph of Oats

"Oats as a human food was discarded in predynastic Mesopotamian times and all through classic times it was held in low repute. . . . The Scythians who ate this 'cattle feed' were decried by the Greeks, as were the Gothonics by the Romans, and the Scots by Johnson. Some physicians in old Rome recognized the great nutritional value of oats, although St. Jerome says, 'only brutes are fed oats.' Today, properly prepared oats are regarded as one of the most nutritious of all cereals!"

—L. B. Jensen. *Man's Foods*, The Garrard Press, Champaign, Ill., p. 79.

Who's Who in Research

"The research worker of the novels and the films is a brilliant young doctor, eating his soul out in general practice till a beautiful girl comes into his life and fires him with the desire for higher things. He sacrifices all his prospects and rents a shed where he toils all day among microscopes and retorts, returning at night dog-tired to his garret and his girl friend. Within six weeks he has discovered the cause of cancer. Real research has been defined as five per cent inspiration and ninety-five per cent perspiration, but the originator of this wisecrack failed to point out that the two are hardly ever produced by the same man. About the only example of a man who was inspired, and then perspired until he succeeded, is Banting. In most cases the brain wave that starts research comes from a man who has not the time, or the inclination, or the damned dull persistence to work it out to a finished project. The translation of the inspired revelations into a solid reality that can be put in bottles and sold over the counter is the work of hundreds of yes-men, each working in a white coat for eight hours a day at some detail of structural formula, repeating the same observation hundreds of times, and handing over his results to someone else."

—Sir Heneage Ogilvie. *The New Zealand Medical Journal* 52: 319–320, 1954.

Editorial

*Diabetic Acidosis**

Optimal therapy of diabetic coma is in a sense largely a public health problem! The fact of the matter is that the major stumbling block in most of our hospitals and practices is the failure to apply properly and accurately even *one* of the many reasonable systems of management. That the proper and accurate application of *one* of these systems is more important for successful therapy than controversies concerning differences among these systems is the contention of this editorial.

Can we plead innocent to the charge that our patients with diabetic acidosis are frequently if inadvertently neglected? I think not. How often is treatment of this medical emergency undertaken, by default perhaps, by an inexperienced interne or resident? How often do practitioners who see diabetic coma once or twice a year, and who in any case are quite insecure in their therapy, assume full responsibility? In my opinion, the incidence of these indiscretions is far greater than many of us might care to admit.

We need not think that the distressingly casual approach to the problem of diabetic acidosis characterizes only certain private hospitals and certain private medical services. Slipshod therapy of this disorder is also a hallmark of some of our major teaching hospitals.

For example, suppose the full-time staff of a given University Department of Medicine is primarily interested in, say, infectious diseases and in diseases of the liver. The latter patients might then receive meticulous attention. The patient with diabetic acidosis, on the other hand, might be uncomfortably regarded as a black sheep who happens along before or after regular working hours. Since such a patient presents no unusual infection or exotic liver disease, therapy can be conveniently directed by a house officer, perhaps one who has just begun his tour of the medical service!

It appears that optimal therapy of diabetic acidosis depends in great part upon attention to and knowledge of detail, upon planning, and upon co-ordination of many services. I believe that the basis for success in this disorder rests upon a scheme in which each patient is carefully followed by experienced and devoted groups of physicians and allied personnel.

For example, in every hospital a team interested in and responsible for the detailed care of *all* patients with diabetic acidosis could be organized. Such a group, depending on hospital size, might consist of at least one physician, several nurses, and a competent laboratory technologist. A conscientious team of this type would soon achieve remarkable facility in providing the best care for the patient with diabetic acidosis. It is clear that planned, centralized, assiduous care of the patient with diabetic acidosis is fundamental to successful therapy.

Many controversies are raging. Should glucose be given early or late; should fructose be used instead of glucose; should potassium be administered routinely? I believe that such controversies sometimes become smoke screens for common, glaring, and sometimes fatal errors: For example, patients with diabetic coma may not receive insulin for several hours after arrival in the emergency room; or

* Presented at postgraduate course in endocrinology sponsored by the University of Buffalo (May 20, 1954).

patients who report obvious symptoms of severe acidosis over the telephone are advised to come in the next morning because of the lateness of the hour; or a responsible physician is not personally checking upon the patient at least hourly until ketosis has largely subsided.

It would seem that our batting average in diabetic coma could be greatly improved if our program included these two vital factors:

(1) Organization of a competent team responsible for all such patients in any given institution.

(2) Following one of the many reasonable systems of management of the disorder.

—Robert Tarail, M.D.
Roswell Park Memorial Institute
Buffalo, N. Y.

Man's Requirement for Vitamin C

The British, who have done such outstanding work in nutrition since the days of John Lind,[1] have carried on this tradition with the publication of a significant study by a subcommittee of the Medical Research Council.[2] The Chairman was Sir Rudolph Peters, and among the committee members was Professor H. A. Krebs of the University of Sheffield.

Twenty conscientious objectors were studied. They received a diet containing less than 1 mg. of vitamin C daily. Three received a 70 mg. supplement of the vitamin daily; seven received 10 mg. daily; and 10 remained unsupplemented.

Clinical signs of scurvy developed in all 10 unsupplemented subjects. The first changes noted were enlargement and keratosis of hair follicles after about 17 weeks of deprivation. Some follicles later became hemorrhagic and developed into characteristic scorbutic spots. Gum changes were seen after 26 weeks of vitamin C deficiency.

Among the other signs noted were pains in the back and limbs, exacerbation of acne, ecchymosis, and knee joint effusion. However, considerable variation in degree was observed. Conventional tests of "capillary strength" failed to show a correlation with the states of vitamin C depletion.

Perhaps the most interesting finding was that 10 mg. of vitamin C daily given to six of the scorbutic subjects removed the clinical signs in all. The skin lesions disappeared in about two months and the gum lesions in three months on this small supplement.

It is significant that the concentration of vitamin C in the white cells appeared to be a useful guide to the state of vitamin C nutrition. The lowest values were reached 3 to 6 weeks before clinical scurvy developed, whereas the *plasma* vitamin C level was practically zero as long as 100 days before clinical scurvy developed.

In the scorbutic subjects, no change in hemoglobin, red or white cell count, or bleeding time was noted.

Experimental wounds were made in the skin of these volunteers and the rate of healing was studied by many techniques, including histologic examination. Delayed healing developed in the deprived group after a long period of time, but not in the early stages. It never developed in the two supplemented groups.

As the report indicates, the fact that a supplement of 10 mg. daily cured clinical scurvy and the fact that 10 mg. of vitamin C daily protected these subjects for periods up to 424 days suggest that the minimum protective dose (as indicated by the signs of scurvy) was in the range of 10 mg. daily. However, certain tests of physical fatigue suggest that the group receiving 70 mg. daily had a better overall performance record than did the 10 mg. group. It is to be expected that the prevention or cure of scurvy is possible on doses less than those necessary for "optimum health."

To satisfy the ill-defined additional needs associated with various human activities and

stresses, the Council recommends trebling the minimum protective dose of 10 mg., thereby confirming the 30 mg. per day requirement recommended in 1938 by the League of Nations Health Organization.

This estimate is less than half the 75 mg. per day recommended by the National Research Council in this country. The latter recommendation is essentially the amount necessary to maintain saturation. However, as the British investigators put it, "as long as there is no evidence to support the view that an intake of more than 30 mg. daily has beneficial effects, there is no basis for recommending an intake greater than that amount."

This excellent study prompts three comments. First, it should be recognized that these observations were made on healthy volunteers. There still is the clear possibility that the presence of a severe illness, associated with general or chronic malnutrition, may alter human metabolism so that the requirement for vitamin C is different from that of these healthy subjects who were ingesting an average of 2900 calories, 100 Gm. of protein, and adequate amounts of minerals and other vitamins.

Secondly, since six months elapsed before even the earliest skin changes appeared in these vitamin C-deprived subjects, shorter periods of deficiency undoubtedly are unrecognized in our present state of imperfect knowledge. This suggests either that "subclinical" scurvy is an entity, or that intakes much below 30 mg. daily are not necessarily detrimental to health.

Thirdly, this study points up the need for future research in the mysterious region between *minimal* and *optimal* needs. Certainly this study has defined the minimal requirement for healthy adults (on otherwise adequate diets). Is there something to be gained in exceeding this amount? Is "saturation" of the tissues necessary? How much is needed for that undefinable state of optimum health?

—S. O. WAIFE, M.D.

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1. WAIFE, S. O.: Lind, Lemons, and Limeys. J. CLIN. NUTRITION 1: 471, 1953.
2. *Vitamin C Requirement of Human Adults*, special report No. 280. Medical Research Council, H. M. Stationery Office, London, 1953.

Announcement

We are happy to announce that, beginning with this issue, the publication of our JOURNAL is under the capable management of the Yorke publishing group, of New York City, publishers of the *American Journal of Surgery* and the *American Journal of Medicine*—the latter popularly known as "the green journal." To signify our new status, our title is now: THE AMERICAN JOURNAL OF CLINICAL NUTRITION.

It is, we think, a testimonial to the growing recognition of the importance of nutrition in medicine that our publishers have made this triad of their former duo. Like Gaul, all medical care is divided into three parts, as indicated by these titles—and the therapeutic triumvirate of medicine, surgery, and nutrition form a union insuring the best in clinical management.

The high standards of the "American" journals are well known to all our readers. We are proud to be titularly associated with them, and we pledge our efforts to the task of keeping our own standards equally high.

We might add that although we are now "American," we are by no means isolationist. We are, as ever, international in our scope, and our pages remain open to contributions from all continents.

—THE EDITORS

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Address all communications dealing with non-editorial matters to American Journal of Clinical Nutrition, Inc., 49 West 45th Street, New York 36, N. Y. Editorial correspondence should be sent, as before, to 133 South 36th Street, Philadelphia 4, Pa.

Dietotherapy

THE LOW PURINE DIET

By Corinne H. Robinson*

The low purine diet has been used by many physicians for the treatment of gout, on the premise that a reduction of purines in the diet would lead to a correspondingly diminished production of uric acid in the body. More recently it has been found that very simple nitrogen- and carbon-containing compounds are precursors of purines which can be synthesized in the body; thus, dietary protein, fat, and carbohydrate all contribute to the production of uric acid. In view of this fact, the exclusion of nucleoproteins from the diet cannot, in itself, be expected to greatly reduce the uric acid levels in the blood and tissues.

Modification of the Diet

If dietary regulation is to be of benefit, it must be observed over a long period of time; some restriction may be indicated throughout life. However, the extremely rigid diets excluding meat at all times which were prescribed some years ago probably were not justified, inasmuch as the patient was likely to become an invalid from his diet as well as from his gout. The following regulations may be of some benefit in the treatment of gout.

Energy

The caloric intake should be planned to sustain optimum weight, or to effect weight loss in the obese. Contrary to popular opinion, obesity is not inevitably present in the gouty patient, nor can it be stated that overweight may predispose to the disease. Nevertheless, an excessive caloric intake will contribute materials for the synthesis of purines in the body.

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Protein

Since the amino acids provide nitrogen as well as carbon for the endogenous production of purines in the body, it is desirable to restrict protein to maintenance levels; that is, to $^2/_3$ to 1 Gm. per kilogram of body weight. This, in itself, dictates an important change in the average American diet, which provides a liberal intake of milk, eggs, cheese, meat, poultry, and fish.

Purines

Some restriction of purines is advisable, so that the uric acid pool is not needlessly increased. All animal foods contain significant amounts of nucleoproteins, while the germ of seeds and some plants also contain nucleoproteins.

These foods are especially high in purines and should be omitted at all times: organ meats—liver, kidney, sweetbreads, brains; meat extracts, meat soups, and gravies; anchovies, and sardines.

Meat, poultry, and fish also contain significant amounts of purines, but indefinite elimination of them does not seem wise. Some patients have benefitted by use of the very low purine diet described below during the acute phases, while the maintenance diet has permitted a small serving of meat three to five times a week.

Other less concentrated sources of purines include whole-grain breads and cereals; dry beans, peas, and lentils; spinach, asparagus, and cauliflower. Their elimination from the diet is perhaps not necessary at all times.

Coffee, tea, and chocolate have been eliminated from the diet by some physicians, since these beverages contain methyl-xanthines. However, methyl-xanthines are metabolized

to methyl-uric acid, which is not believed to increase the deposition of urates in the tissues. Thus, the omission of these beverages from the diet of persons who desire them imposes a needless hardship.

Fat

Since a high-fat diet may interfere with the excretion of urates, the fat level should be restricted to that provided in the basic diet pattern.

Carbohydrates

Carbohydrates are used to complete the caloric requirement. A plan for the low purine diet is presented below:

LOW PURINE DIET

Suggested Basic Foods

3 cups milk
2 eggs
1 ounce cheese
1 serving enriched cereal
4–6 slices enriched bread
3–4 servings vegetables including:
  1 medium potato
  1–2 servings green leafy or yellow vegetable
  1 serving other vegetable
2–3 servings fruit including:
  1 serving citrus fruit
  1–2 servings other fruits
2 tablespoons butter or fortified margarine

Additional calories are provided as needed by increasing the amount of potato, potato substitutes such as macaroni, rice, noodles, fruits, vegetables, bread, sugars, and sweets.

Nutritive Value of Basic List of Foods: Calories, 1850; protein, 68 Gm.; fat, 80 Gm.; carbohydrate, 220 Gm.; calcium, 1400 mg.; iron, 11.3 mg.; vitamin A, 10,350 I.U.; thiamine, 1.32 mg.; riboflavin, 2.33 mg.; niacin, 10.0 mg.; ascorbic acid, 145 mg.

Moderately Low Purine Diet

Use a small serving of lean beef, veal, lamb, poultry, or fish three to five times a week. On the days when these are included, the cheese and one egg may be omitted.

One of many ways in which the basic list of foods might be used to plan meals is suggested here.

Suggested Meal Pattern	*Sample Menu*
Breakfast	
Fruit	Orange juice
Enriched cereal	Cream of wheat with milk, sugar
Milk and sugar for cereal	
Egg—1	Shirred egg
Enriched toast—2 slices	Toast—2 slices
Butter—2 teaspoons	Butter
Coffee—1 cup	Coffee with milk, sugar; no cream
Luncheon or Supper	
Cream soup	Cream of tomato soup; Melba toast
Egg or cheese	Fruit salad plate with:
Salad	Apricot halves Strawberries Banana wedges Cottage cheese center Lettuce, watercress French dressing—1 tablespoon only
Bread—2 slices	Plain muffin with 1 teaspoon butter, current jelly
Butter—2 teaspoons	
Fruit	
Milk—1 cup	Milk—1 glass
Dinner	
Egg or cheese	Cheese soufflé
Potato	Baked potato with 1 teaspoon butter
Cooked vegetable	Broiled tomato
Bread—1–2 slices	Hard roll with 1 teaspoon butter
Butter—1 to 2 teaspoons	
Dessert	Raspberry sherbet
Milk	Milk

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Nutrition News

☆ *News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the* JOURNAL.

Vitamin E Congress

The Third International Congress of Vitamin E will be held in Milan, Italy, early in September 1955. Consideration will be given to the relation of vitamin E to: (1) metabolic processes; (2) vascular physiology and pathology; (3) neuromuscular system; (4) other vitamins and hormones.

Scientific communications addressed to the Congress must be received before March 1, 1955, and should include two summaries of one page or less, of which one must be in English.

All communications should be addressed to the Secretary of the Congress, Prof. Emilio Raverdino, via Pietro Verri 4, Milan.

The other officers of the Promotion Committee are Prof. Carlo Foà, President, and Profs. Pietro Rondoni and Emilio Trabucchi, Vice Presidents. They have been assisted in their planning by Italian specialists in vitamin E, and the participation of leading scientists from other European countries, England, and America is anticipated.

Endocrinology Congress

The Third Panamerican Congress of Endocrinology will convene this year in Santiago, Chile, on November 21–27. Participants include B. A. Houssay, H. Selye, and H. M. Evans, among many other distinguished workers from the three Americas.

Requests for information on attendance, submission of manuscripts, etc., should be addressed to Dr. Arturo Atria, Secretary General of the Congress, Casilla 70 D, Santiago, Chile.

Nutrition Briefs

CURRENT OBSERVATIONS OF CLINICAL INTEREST

Severe and prolonged choline deficiency in rats with associated hepatic disease did not affect the rate of absorption of oil, degree of hydrolysis of intestinal fat, or the level of serum lipids.

J. Ward, R. Haslam, and L. Schiff. *Proc. Soc. Exper. Biol. & Med.* 85: 401, 1954.

Pantothenate-deficient rats may lose their innate specie-resistance to infection with a type of corynebacterium pathogenic for mice. Ordinarily, this bacterium is held to be nonpathogenic for rats. In the presence of pantothenate deficiency, however, the animals become quite susceptible to its infection.

T. F. Zucker, and L. M. Zucker. *Proc. Soc. Exper. Biol. & Med.* 85: 517, 1954.

Glucose, biotin, para-aminobenzoic acid and methionine were administered to starving albino rats infected with one million parasites. Glucose or biotin did not in any way influence parasite growth in starving animals. In animals given PABA or methionine during starvation, enhanced growth of parasites was seen as compared to that in controls. The growth was appreciably higher in the methionine series.

S. P. Ramakrishnan, S. Prakash, A. K. Krishnaswami and C. Singh. *Indian J. Malariology* 7: 225, 1953.

Rats on a high carbohydrate regimen inadequate in thiamine succumbed in 75–85 days. After death, slight degeneration in the visual pathways was observed. Deficiency of riboflavin produced no changes in the visual pathways and the rats in this group survived past 220 days. In deficiency of both vitamins, rats survived to 200 days, but with gross lesions in the visual pathways. In rats rendered severely deficient in thiamine (by analogue administration) and riboflavin, no signs of visual pathway degeneration appeared.

F. C. Rodger. *Brit. J. Ophthal.* 38: 144, 1954.

Nutritional Quotes

Antibiotic Avitaminosis

"Research carried out in our clinic documents the strict relationship which exists between antibiotics and vitamins. We have been able to show that some antibiotics, both in animals or in sick or healthy humans, cause the complete, or almost complete, sterilisation of the intestinal contents; parallel to this there is a progressive diminution in the vitamin content of the organism, sometimes with appearance of corresponding clinical symptoms. These avitaminotic manifestations may be inhibited by the preventive administration (parenteral) of vitamins of the B group. . . .

An entirely new piece of evidence has emerged from our research. This concerns the alteration of intestinal function and absorption after administration of antibiotics; such a fact is of great importance in vitamin metabolism. We have shown that alterations occur in the motility of the intestine, segmented dystonia being noted, with the transitions generally accelerated; alterations in the absorption of glycides, lipides and iron also occur. At the present moment the cause of these alterations is not known; it may be considered that under normal conditions the intestinal bacterial flora succeeds in influencing the trophism of the intestinal walls either by means of the elaboration of vitamins, or by impeding the development of monilial type fungi, or by other means, thus safeguarding the normal course of some of its functions."

—V. Chini in an address presented at the 3rd Science Day, Milan, April 12–16, 1953, on "Vitamin Requirements and Antibiotics." (Abstracted in *Acta vitaminol.* 7: 69, 1953.)

Cholesterol Absorption

"The average adult consumes about 400 to 500 mg. of cholesterol a day along with a very variable amount of plant sterols. Most of the latter are poorly absorbed. The absorption of cholesterol is augmented by fat feeding, in animals at least. Most of the cholesterol is absorbed by lymphatics—for which bile is necessary—and is carried in the plasma in combination as alpha and beta lipoprotein. On normal diets, absorption is probably something of the order of 70 to 95 per cent efficient."

—I. H. Page. *Circulation* 10: 1, 1954.

Diet and Activity

"The occupation at which a person earns his living may be a poor indication of his nutritional requirements, and in calculating such requirements, should never be considered apart from the manner in which he spends his leisure."

—R. C. Hutchinson and W. A. Krehl. *Borden's Review of Nutrition Research* 15: 49, 1954.

For Afternoon Alertness

"To prevent the feeling of drowsiness, lack of coordination, and disinclination for physical or mental activity following the consumption of a large mid-day meal, there is evidence that, for sedentary work, the size of this meal should not exceed 9 to 12 ozs."

—R. C. Hutchinson and W. A. Krehl. *Borden's Review of Nutrition Research* 15: 50, 1954.

Linked Deficiencies

"But in ordinary life, deficiency of vitamins will almost never occur without simultaneous deficiency of structural material, particularly of calcium and protein, and it will be impossible to remedy deficiency of protein or calcium with any natural food without adding at least the B vitamins."

—A. M. Thomson. *Nutrition Abstracts and Reviews* 24: 15, 1954.

Idiosyncrasy in Vitamin D Intoxication

"In more than 20 years of practice in pediatrics I have observed that the tolerance of infants to massive doses of the antirachitic vitamin varies from child to child. Because of this, whilst some subjects support quite well the repeated administration of 600,000–800,000 units of vitamin D, others suffer from diarrhoea, dyspepsia, anorexia, and loss of weight after having taken the contents of only a single ampoule. If the vitamin is given by injection, hyperthermia may occur, even to a serious degree, although of brief duration; this may be accompanied by intolerance phenomena such as nausea and lack of appetite. It is therefore advisable to be extremely prudent in the administration of massive doses of the antirachitic vitamin; semi-massive doses are to be preferred."

—F. Borsarelli in an address presented at the 3rd Science Day, Milan, April 12–16, 1953, on "Hypervitaminosis by the Antirachitic Vitamin." (Abstracted in *Acta vitaminol.* 7: 87, 1953.)

Reviews of Recent Books

Nutrition and Physical Fitness (sixth edition) by L. Jean Bogert, Ph.D. W. B. Saunders Co., Philadelphia, 1954, pp. 664, $4.50.

The fact that this volume is now in its sixth revision since it first appeared in 1931 attests its value. Careful perusal confirms and amplifies this conclusion. It is a comprehensive text presenting the essentials of nutrition accurately, clearly, and concisely. It can be studied with profit by all those concerned with nutrition (and what adult isn't concerned, at least with his or her own nutrition?), nurses, college students, dieticians, graduate students, mothers, and physicians. Without exhausting the reader, the established knowledge concerning nutrition is made palatable and understandable.

In the preface to the first edition Dr. Bogert states that the purpose of the book is threefold: (1) To gather in a single volume facts useful in meeting everyday problems of nutrition; (2) To make this information widely available by presenting it in simple language to those with no prior knowledge of chemistry; and (3) To emphasize wherever possible where and how a knowledge of nutrition contributes to health. These three objectives are fully attained. The book may be used as a text in teaching and is equally valuable as a reference volume of basic information, for it is adequately indexed.

The contents, 29 chapters and an appendix of tables delineating the nutritive value of foods, is divided into four parts: I, Body Needs; II, Body Processes; III, Meal Planning; and IV, Diet for Special Conditions. In addition to specific reference footnotes documenting many statements, a fairly comprehensive and well-selected list of articles and/or books for supplemental reading ends each chapter.

Typography is clear; the illustrations are appropriate and informative. For professionals the chemistry is unnecessarily elementary, but the reason for this, as stated in the text's preface, appears valid. This is a storehouse of essential information, so organized that it is readily accessible to the novice, advanced student, nurse, or busy medical practitioner.

EDWARD J. STIEGLITZ

Energy Metabolism and Nutrition by R. W. Swift and C. E. French, The Scarecrow Press, Washington, D. C., 1954, pp. 260. $5.75.

The authors of this book are from the Department of Animal Nutrition of the Pennsylvania State University. They have prepared a useful survey of the principles and methods of study of energy metabolism and present their material from the standpoint of the teacher of senior and graduate students.

The first part deals with principles of calorimetry, and there is a discussion of the respiratory quotient, body temperature regulation, and so on.

The second part deals with the methods used in direct and indirect calorimetry and in the study of energy metabolism made from the determination of digestibility, dynamic effect, and net energy.

The third part deals with methods of food experimentation in which the length of experimental periods, the evaluation of the procedure, basal metabolism, obesity, work efficiency, and efficiency of utilization are briefly discussed.

While there is nothing very new in the book, it is of definite value for those whose work involves these problems, since it has within its covers most of the essential information needed for workers in the field. In the reviewer's opinion, it does achieve its goal of offering a useful guide to relatively inexperienced students of biochemistry and physiology who are interested in energy metabolism and who want to understand the principles of theory and practice in this field.

A.E.S.

Vitamins and Hormones, Vol. XI, Academic Press Inc., New York, 1953, pp. 356, $8.50.

These annual compilations of monographs have come to be one of the best sources of summarized information available in clinical and laboratory investigation. The 1953 volume is no exception. Among the eight chapters, our readers will find of particular interest that by Nicholaysen and Eeg-Larsen of Oslo on vitamin D, A. P. Meiklejohn on ascorbic acid, Ralli and Dunn on pantothenic acid, and Zubiran and Gomez-Mont on "Endocrine Disturbances in Chronic Human Malnutrition."

The latter paper is a stimulating survey of disturbances of the endocrine system found in 529 adults suffering from chronic malnutrition. Autopsy material revealed involution and atrophic changes in the endocrine glands; and a large number of hormonal determination and endocrine function tests showed diminished activity in most instances. With improvement of nutritional status, normal function was reestablished in most cases. It appears that lower pituitary activity is the fundamental cause of the disturbances of the other endocrines.

The liver had been considered to have a cardinal role in hyperestrogenism in malnutrition. However, in this study, no such phenomenon was present in

nearly 100 per cent of the women or in 79 per cent of the men suffering from severe malnutrition. In fact, in nearly every instance an increase in estrogen activity was observed during the recovery period.

Other articles deal with the synthesis of cortisone, the cytological localization of ketosteroids, and the biochemistry of the thyroid gland.

This book, with its useful author and subject index, can be highly recommended. S.O.W.

Newer Concepts of the Causes and Treatment of Diabetes Mellitus. The National Vitamin Foundation Inc., New York, 1954, pp. 177, $2.50.

This is a report of the proceedings of the symposium on diabetes sponsored by the New York Diabetes Association in October 1953. The arrangement is such that the first portion of the proceedings deals with the fundamental biochemical advances and recent experimental data in diabetes; the final sections are devoted to clinical applications of this newer knowledge. Among the contributors to the first part are some of the outstanding investigators in this field: Mayer discusses the Hereditary Obese-hyperglycemic Syndrome in the Mouse; Gurin, Lipogenesis in Diabetes; Long, The Endocrines and Carbohydrate Metabolism; Houssay, Hormone Interrelationships; Stadie, The Action of Insulin; and Wrenshall, Glucagon.

In the second part of the book, the clinical aspects of diabetes mellitus are given broad coverage without emphasis on detail but with attention to general concepts adopted by the individual authors. The reader may take exception to some of these presentations based upon his own experience and practice in this field. The recommendation by Pollack that patients be permitted to use free sugar represents a departure from the usual practice. The discussion of Pregnancy and Diabetes by Hurwitz reviews his experience in the management of 140 such patients, emphasizing the need for careful and meticulous supervision by the internist and obstetrician. Following this and other chapters there are included the discussions presented by those attending the symposium, which adds to the value of this report. The book should be read by all physicians interested in this disease and its treatment. C. R. SHUMAN

Wine as Food and Medicine by S. P. Lucia, Blakiston, New York, 1954, pp. 119, $3.00.

This book is almost a polemic on the virtues of wine. It is a compendium of old and new (mostly old) claims of the nutritive and curative powers of fermented grape juice.

Although the author states there is a "demand for an evaluation of wine as a medicinal agent, and for the separation of fact from folklore," we also read in the next paragraph that "partaking of wine offers an opportunity for psychic rest and release from the pressures of the day; it also provides time for recovery from mental fatigue so that the psyche may be better able to cope with our frenetic mode of living." This sentence shows the viewpoint and style of the book. The single slant is also clearly demonstrated in the following. "This book is offered as a *vade mecum* to those who are unprejudiced in their search for that which makes men desire to live against odds often unsurmountable."

This reviewer enjoys Claret and Chablis as much as anyone, but he does not feel relieved that all will be well by reading a 1929 reference that "under normal conditions, wine included discreetly in the diet does not produce hepatic lesions." Neither is he convinced that minor hepatic insufficiency responds "not unfavorably to unadulterated dry white table wine" (page 58). He remains unmoved by a sentence from a 1939 reference that "For the laborer who uses his muscles, it [wine, of course] even may be a physiologic necessity!" (exclamation mark and all).

The reviewer is even less happy about the discussion of the use of wine in diabetes. There is a quotation, for example, from a paper written 45 years ago that wine does not increase glycosuria. The uncritical inclusion of statements on the virtues of wine can be illustrated (page 96) by four old references purporting that significant *de*creases in blood sugar levels occurred in diabetics after "small amounts" of alcohol.

Throughout the book are such statements as: a glass of wine taken at bedtime will often forestall a cold by acting as a sudorific—or, in endogenous obesity, white wine is preferred because of its diuretic properties and stimulating effect on neuromuscular tone.

There is a clear need for a critical analysis of the huge volume of claims and "observations" about wine as a food or drug. That particular goal is not achieved by this paean of praise of the virtues of the elixir of the grape. A.E.S.

Annual Review of Medicine, Vol. 5, edited by W. C. Cutting and H. W. Newman, Annual Reviews, Inc., Stanford, 1954, pp. 490, $7.00.

The current edition of these "Annual Reviews" maintains their distinctive characteristics: summaries of current developments in various fields of medicine documented by hundreds of bibliographical references. For example, Soffer and Gabrilove's review of endocrinology, excluding the gonads, documents 433 articles. Although many papers are summarized, at times in but one sentence, the overall picture of today's research is quite clear.

There are chapters on radioactivity, toxicology, dentistry, and psychiatry, as well as on the usual subjects, such as cardiology, infectious diseases, etc. All are written by experts in their respective fields.

Again, this review will be of particular benefit as a helpful reference volume and will be especially useful to those in investigative work. S.O.W.

Abstracts of Current Literature

NUTRITION: SURVEYS AND STUDIES

Several reviews dealing broadly with the nutritional aspects of medicine have appeared in the recent medical literature. The articles noticed below are strongly recommended to our readers.

Nutrition in Clinical Medicine. T. B. Van Itallie, J. Mayer, and F. J. Stare. *New England J. Med.* 250: 199, 1954.

This review, buttressed by 98 references, deals with aspects of supportive and therapeutic nutrition. Factors affecting protein utilization during convalescence are discussed. These include carbohydrate intake, fat intake, caloric intake, protein stores, rate, timing, and route of administration of nutrients, potassium intake, trauma, and infection.

Celiac disease, uremia, diabetes mellitus, and obesity are the topics discussed under the therapeutic aspects.

In total starvation body protein is broken down to meet the caloric requirement. Even a small amount of ingested glucose (100 Gm./day) diminishes protein loss by 50 per cent. Fat will decrease protein breakdown in a rat fed 25 per cent of the caloric requirements. When protein stores are not depleted and if the animal is receiving enough essential carbohydrate and protein, the caloric intake is the most important factor in protein utilization. Under these conditions the energy requirement is met at the cost of the protein reserves. This effect of caloric insufficiency on the protein is important when the protein stores are not excessively depleted. As the stores become depleted the role of caloric intake on protein utilization becomes less important, and the body holds on tenaciously to its protein until the fat stores are depleted. In this situation it is more important to feed a higher proportion of protein.

Fed or infused amino acid hydrolysate is better utilized when glucose or fat is given with it. The body carbohydrate and protein requirement can be met by infusion, though it is difficult to supply caloric need by this method. To prevent sclerosing of the vein it is necessary to give isotonic solutions of glucose, which involves administration of large volumes of fluid. This problem can be avoided by infusing fat emulsion. The difficulty of manufacturing, transporting, and storing this emulsion has limited its clinical use. Fructose has been studied as a possible infusion sugar. Evidence indicates that it may be better retained by the body than glucose and can be infused more rapidly.

Potassium is very often overlooked when a patient is maintained by intravenous feeding. When the infusion mixture contains potassium there is better utilization of the infusion materials.

After a surgical operation a patient usually goes through four phases of recovery. In the first stage there is a period of nitrogen loss. It is not clear whether parenteral infusion of amino acids is desirable or not in this stage. Following this there is a stage of decreased nitrogen loss, an anabolic stage, and finally a fat gain phase. During the anabolic phase it is important that intake of protein and calories be adequate.

A relation has been shown between celiac disease and the presence of wheat in the diet. The source of trouble seems to be in the protein fraction of the flour, probably gliadin. Patients with this disease seem to have trouble in absorbing saturated fat; how-

ever, when fed unsaturated fats, fat absorption becomes normal.

Uremia is relieved by a diet high in calories and low in protein. The patients, though usually nauseated, will take frozen butter pills filled with sugar or an emulsion of butter, sugar, and a little flour, flavored with coffee extract.

A case of a patient with diabetes mellitus is described in which a high fat diet was eaten for a period of 29 years with no ill effects. The use of fructose in diabetes is also discussed. It seems to be utilized normally in diabetes.

The final subject discussed is obesity. The use of body weight, fat-fold thickness, body density, and body water volume in determining body composition is discussed. The treatment of obesity has been hampered by lack of understanding about its etiology. Genetic, traumatic, and environmental factors may play possible roles in the development of obesity. The authors thought that valuable information might be supplied if type of fat distribution and age of onset of obesity were studied.—M. W. Bates

Trends and Needs in Nutrition. W. H. Sebrell, Jr. *J. A. M. A.* 152: 42, 1953.

This is an interesting review of the current trends in clinical nutrition, and was the response of Dr. Sebrell to the presentation of the Goldberger Award of the American Medical Association for outstanding and sustained work in the field of clinical nutrition. It should be read by all clinicians.—S. O. Waife

The evaluation of nutritional problems on a broad scale throughout the world is an extremely important part of the work of several agencies. It is vital that the clinical aspects of these nutritional programs continue to receive attention, as in the following reports.

Developing Modern Nutrition Programs. W. H. Sebrell. *Pub. Health Rep.* 69: 277, 1954.

To establish any nutritional program it is necessary to appraise the nutritional status of the population by a dietary survey which is integrated with a clinical study. From this appraisal dietary deficiencies can be determined. When this is done, the reason for the deficiency can then be sought. It is important to correct the malnutrition and to prevent further nutritional problems by improving the dietary pattern of the population, using such methods as education, legislation, and food enrichment.

The development of such a nutritional program requires integration among various branches of health service and government departments.

Periodic assessment of the program is necessary in a long-range program to re-evaluate nutritional problems—M. W. Bates

Reports from the Americas on Nutrition Programs. *Pub. Health Rep.* 69: 284, 1954.

This report is a summary of replies to questionnaires sent to countries of North and South America. Replies were obtained from 37 countries and territories, though not all were received in time for this report. The following subjects were considered: endemic goiter, kwashiorkor, dietary surveys, clinical studies, laboratory studies, statistical data relating to distribution of population and distribution of food, nutrition education, dietary supplementation, and training of personnel.—M. W. Bates

Fortification of foods to provide better nutrition for large segments of the world's population is an important problem. Inexpensive yeast preparations and algae protein, in addition to vitamins, may prove to be valuable forms of supplementation of diets as the world population increases.

The Addition of Specific Nutrients to Food. *Pub. Health Rep.* 69: 275, 1954.

In the early 1930's synthetic vitamins were added to food to correct nutritional deficiencies which were then prevalent in the United States. This was done with little or no supervision. In 1939 and 1946, policies were adopted on the proper addition of nutrients. These policies are revised and restated in this paper by the Food and Nutrition Board and the Council of Foods and Nutrition. The addition of nutrients is endorsed if an increased intake of the nutrient is advantageous, if the selected food is a proper vehicle, and if such an addition would not prevent a diet good in other respects. It is more desirable to meet requirements using natural foods, preserving nutrients already present by better production, processing, storage, and distribution. The food selected as vehicle should preferably be one in which a nutrient loss has occurred. The addition of nutrients normally not found in the food might be valuable if no better way was found of presenting it to the public.—M. W. Bates

An authoritative review of the human nutritional requirements and a practical discussion of these problems are found in the following paper.

Human Nutritive Requirements and Recommended Dietary Allowances. G. A. Goldsmith. *J. Am. Dietet. A.* 29: 109, 1953.

Nutritive requirements depend on age, sex, body size, and physical activity, and may be increased by physiologic stress of growth, pregnancy, lactation, and many disease states. Dr. Goldsmith presents a logical, concise, lucid explanation of the philosophy and experimental bases underlying the National Research

Council Recommended Allowances. The differences between minimal requirement and allowances for good nutritional status are discussed. United States, British and Canadian standards are compared for calories, protein, vitamin A, thiamine, riboflavin, niacin, and ascorbic acid. It is emphasized that these standards were formulated for planning and evaluating food supplies for individuals or population groups. The NRC allowances are high enough "to cover substantially all individual variations in the requirements of normal people," including a margin of safety above the critical or minimal level to permit additional benefits. These allowances were *not* formulated to provide a basis for judging the nutritional status of populations. According to the author, persons whose consumption equals or exceeds the goals presumably are adequately nourished but not all persons who fail to reach the goal are malnourished.

Calcium needs are now under review, and data concerning riboflavin and niacin need extension by more research. In the revision of the Recommended Dietary Allowances which is under study, consideration will be given to pyridoxine, pantothenic acid, and vitamin B_{12}, in addition to the nutrients discussed in the 1948 publication.

Knowledge of *minimal* requirements is especially important in planning food supplies for emergency situations. Drastic reduction in food intakes for a few days or even weeks is tolerated reasonably well except by infants, lactating women, the sick and injured, and those engaged in heavy work. In any prolonged period of food shortage, frequent examination of the population by trained survey teams is recommended.

This article is a positive contribution to nutrition literature with its up-to-date bibliography and its impartial presentation of experimental evidence underlying the choice of our present recommended allowances of nutrients.—J. SMITH

The metabolic response to stress is exceedingly complicated and is being dissected by many investigators at the present time. From the standpoint of the nutritionist, it is important to be familiar with the requirements for protein, calories, and accessory food factors during periods of physical and mental stress.

Stress and Nutrition. C. F. Gastineau. *J. Am. Dietet. A.* 29: 666, 1953.

This is a review of the literature pertaining to the importance of nutrition during conditions of stress. Surgical operations, burns, industrial and war wounds, climate variation, and high altitude flying are considered as types of stress. After almost any sort of injury or illness there is a loss of stores of body protein (which may reach 44–62 Gm. protein daily), and this loss must be restored by an adequate diet during convalescence. Opinions differ as to whether and to what extent the loss of body protein can be prevented by a generous supply of calories and protein given immediately after injury. Attempts have been made to prepare stable emulsions of fat for intravenous feeding so that protein can be spared from having to be used for energy and so that the volume of fluid can be cut over what is necessary when carbohydrate is the predominant source of energy.

The mechanism of the metabolic changes in stress is not clear. The adrenal cortex appears not to be the prime mover but more likely plays a necessary and modifying role. If ACTH or cortisone is given to a patient already showing stress of illness or injury, the nutritional problem may be further complicated. It is particularly important for this patient to consume a diet adequate in calories and proteins. Under some circumstances, restriction of salt or added potassium may be necessary.—J. M. SMITH

The problem of feeding large numbers of people during periods of emergency is reviewed in the following article.

Disaster Feeding. J. M. Hundley. *J. A. M. A.* 151: 1404, 1953.

This article is a good review of the problems in civilian defense that relate not only to nutrition for those unable to provide for themselves, but to emergency feeding as a powerful tool for calming disturbed or panic-stricken populations. Probably the effect of adequate feeding on morale is more important than its physiological effect, especially the first few days of a disaster.

A top priority should be given to the provision for an emergency supply of potable water. From experiences at Hiroshima and elsewhere, it appears that the initial stress has the effect of dividing the population into three groups. The minority, 10 to 25 per cent, who are in full possession of their mental and emotional faculties; the majority, perhaps 75 per cent, who show some inadequacies in their reactions, such as signs of fear and reflex behavior; and another minority group, 10 to 25 per cent, who are grossly incapacitated by emotional disorganization. In the second phase there is a gradual return of self-consciousness and awareness in the majority of the population, but feelings of anxiety, fear, and anger develop. During this period, when attention is directed toward finding relatives, or seeking shelter or care, many can be favorably influenced by a blanket or a cup of coffee. The facility which allows the administration of coffee or warm food is tangible proof that the community is still functioning and does a great deal to reduce panic. In the first few hours after a disaster, a stimulating beverage—hot coffee among American populations—would be most welcome. Infants and children should have milk. Food provided

for more prolonged emergency feeding should be familiar and well liked, with a high general acceptability. In disaster, and in similar states of stress, there is a tendency to reject unliked or unfamiliar food to an even greater extent than under normal conditions.

From experiences in Great Britain, it was noted that a deficiency of calories was reflected with surprising speed, in that morale was affected rapidly. There was discontent, grumbling, and irritability, signs associated with the reduction in caloric intake of about 20 per cent.

This paper will be of interest to all physicians. —S. O. WAIFE

The nutritional requirements for the athlete do not appear to be different from those of other individuals engaged in strenuous activities, judging from the observations recorded in the following paper.

Nutrition of Athletes. H. L. Upjohn, J. A. Shea, F. J. Stare, and L. Little. *J. A. M. A.* 151: 818, 1953.

There is much theory and little fact about the nutritional needs of athletes. At some training tables pork may be taboo, or the fat of beef is removed. Typically, candy is bad; there is to be no drinking or smoking; pastry is out except at dinner; and no jelly is served with bread. Fried foods are avoided. These, and other lists of prohibitives, apparently have no evidence to support their existence.

Since there are no magic foods that produce superpower or agility, it would seem logical that the same meats, milk, eggs, vegetables, fruits, and breads that are fundamental to the health of every person are needed by the athlete. However, because his energy output may be much larger, the athlete would have to increase his caloric intake. Regardless of the weight of the athlete, and whether he must gain, lose, or maintain it, the authors of this paper recommend a large serving of a protein, two or more glasses of milk, and a well-balanced diet with vegetables, fruits, and whole grain breads and cereals. Milk is no more a necessity in the diet of the athlete than for any other person. Vitamin supplements are an unnecessary expenditure to the average athlete. There is ordinarily no reason for trouble with fried foods.

Because a tendency to gain weight is a real problem to some athletes at the training table, those foods that pack calories in the form of concentrated sweets, rich desserts, and gravies, should be served sparingly to those individuals.

Most people agree that it is not good to eat immediately before or after exercise. Neither should large amounts of fluid be consumed just prior to or after strenuous activity. The authors describe the type of menu that might be served to athletes where the chief athletic activity varies from morning to evening. Sucking a cool orange at half-time quenches thirst, tastes good to most persons, supplies a small amount of glucose for energy, but particularly makes a contestant happy and helps him to relax.

The authors conclude that "eating is partly habit and must be treated as such. There is much to be gained in understanding a player's nutritional problems, for it is not easy to break life-long habits."—S. O. WAIFE

There is a wide divergence of opinion concerning the nutritional requirements in pregnancy. Some authorities state that there is an increased need for protein and calories in all pregnant patients in order to prevent the obstetrical complications of toxemia, premature delivery, and increased neonatal mortality. However, there is no unanimity of opinion on this point. If malnutrition has existed previous to pregnancy, or develops during pregnancy due to a reduction in food intake, clinical and biochemical alterations will appear, just as they would in nonpregnant individuals. However, it cannot be denied that there are augmented protein and calorie needs for the conduct of a normal pregnancy.

Physiological Adaptation and Nutritional Status During and After Pregnancy. I. G. Macy and associates. *J. Nutrition,* Supplement 1, 52: 1–91, 1954.

This report by Icie G. Macy and associates is in the form of a monograph as a special supplement to volume 52 of *The Journal of Nutrition* and constitutes the most comprehensive clinical investigation in this field.

This investigation is concerned with 1064 pregnant patients (378 white and 686 Negro) who were chosen for study from three socioeconomic groups, namely, a public prenatal clinic for low-income and indigent populations (Group A), a private prenatal clinic for families with moderate means (Group B), and a group of private patients, characterized as middle-class with a few wealthy individuals (Group C). It contributes to the scope of knowledge of the mean and range normality standards of physiological and chemical variations of women during childbearing, and some of the factors that may augment or decrease them. It presents, for the first time, average and range normality standards of 6 blood components determined on single samples of blood collected successively following conception, and demonstrates a specific physiological course of uncomplicated pregnancy and parturition of 427 mothers and their respective, full-term newborn infants. The blood components determined were hemoglobin, sera total protein, vitamin C, vitamin A, carotenoids, and alkaline phosphatase. These constituents represent various developmental and functional processes and participate in several body systems.

Clinical, biochemical and dietary intake assessments agree in indicating that lower income, in-

ferior dietary intake, and patient-choice of substandard prenatal care are reflected in objective biochemical blood concentration levels considered to be in the direction of concentrations incompatible with healthful living.

Twice as many of the diets of the white patients in Group A were classified as incompatible with health when compared with white individuals in the selected and higher socioeconomic Groups B and C, inasmuch as the nutrient intake was less than 60 per cent of the recommended dietary allowances. While it is known that the recommended dietary allowances of the National Research Council represent not merely minimum requirements of average individuals, but levels enough higher to cover substantially all individual variations in the requirements of normal people, it is evident that dietary intakes carrying less than 60 per cent of the essential nutrients might be inadequate for many women under the stress of pregnancy.

All of the Negroes, including those in the selected group, had substandard dietary ratings comparable to the low-income whites in Group A. While it is important to point out that white and Negro pregnant women in the low-income Group A shared equally with Negroes in the private clinic Group B in the disadvantages arising from inferior diets, it is of equal importance that marginal diets are usually not of short duration but arise from long-standing unsatisfactory economic conditions or undesirable dietary habits. The biochemical findings in the case of some blood components would indicate that undernutrition is likewise of long duration, probably existing at the time of conception. Should this be the case, there are superimposed upon the usual augmented needs of reproduction, additional nutritive demands for purposes of conditioning or reconditioning the maternal body.

Health authorities are challenged to determine whether racial differences observed between white and Negro subjects are truly racial or whether improved nutritional status of the Negros of this country will tend to lessen or nullify the differentials observed between the two races. Multiple deficiencies due to inadequate or unbalanced diets of long duration are reflected in inferior health and are difficult to replete, especially in adolescence and young adulthood, and may have more serious consequences upon the outcome of pregnancy if malnutrition exists at conception or during the first trimester of pregnancy when organ differentiation is taking place in the fetus. These may account for some of the restricted and variable physiological responses in the Negro race and low-income white groups.—B. SURE

The Vanderbilt Cooperative Study of Maternal and Infant Nutrition. W. J. Darby and associates. *J. Nutrition* 51: 539, 1953.

The background, design, methodology, and population sample of a study of nutrition in pregnancy are described. This study embraced 2338 pregnant white women cared for in the prenatal clinic of Vanderbilt University Hospital during the period from September 1945 to February 1949. The limited available data on nutritional assessments of pregnant or lactating women with the general population of the region are summarized.

The nutritional characteristics revealed by records of dietary intake, laboratory assessments, and physical examinations are described for an unselected group of 2129 pregnant white women. These findings are discussed in relation to the altered physiology of pregnancy.—B. SURE

OBESITY

The perennial problem of obesity continues to provoke discussion and, fortunately, research. Recently several papers have described investigations on the relationship between food intake and body temperatures.

A Mechanism of Regulation of Food Intake. J. L. Strominger, and J. R. Brobeck. *Yale J. Biol. & Med.* 25: 383, 1953.

This paper presents the thesis, together with some evidence from the literature, that the ability of animals to alter their food intake when the composition of food is altered is due to their recognition of some "intrinsic" factor. Apparently this is not the caloric value of the food. It is hypothesized that this factor may be identical with the specific dynamic action of food.

The authors clearly state that their data do not exclude the possibility that there are other modes of regulation. In their scheme, any increase in the total amount of heat in the body, acting through thermal gradients and receptors, would initiate impulses inhibiting the mechanisms responsible for feeding. Thus, an increase in environmental temperature would do the same.—S. O. WAIFE

Regulation of Food Intake in Normal Rats and in Rats with Hypothalamic Hyperphagia. J. L. Strominger, J. R. Brobeck, and R. L. Cort. *Yale J. Biol. & Med.* 26: 55, 1953.

In a companion paper, the Yale investigators furnish the experimental data for the SDA (specific dynamic action) concept of regulation of food intake. Both long- and short-term studies in rats, following dilution of a stock diet with fat, protein, carbohydrate, water, and cellulose, indicate that caloric value is not the "intrinsic" food factor which rats invariably recognize. In experiments involving a suboptimum concentration of dietary protein, the body weight was governed by the total protein in-

take and influenced by the metabolic uses of the protein synthesis, deamination, or gluconeogenesis.

Obese rats with hypothalamic hyperphagia did not adapt their food intake in the normal manner when the diets were diluted with fat or cellulose. These animals failed to recognize the change in the organism produced by the dietary alterations.—S. O. WAIFE

Hyperthermia in Hypothalamic Hyperphagia. J. Mayer, and R. M. Greenberg. *Am. J. Physiol.* 173: 523, 1953.

The conclusions of Brobeck *et al.* (q.v.) are questioned by these Harvard investigators, who measured the colonic temperatures of rats made hyperphagic by hypothalamic injury. Such animals were found to have significantly higher temperatures than operated and nonoperated controls. Apparently, this finding was not due to the nutritional state, to obesity *per se*, or to a breakdown of the mechanisms regulating body temperature. These authors feel that while the data indicate that "animals do not eat to keep warm," no obvious explanation is available.

Because of differences in experimental procedures and other variables, these findings do not necessarily contradict those previously noted. Indeed, if hypothalamic hyperphagic animals have their hypothalamic thermostat set too high, they would eat more (particularly protein, for its SDA) to maintain this (slightly) higher body temperature.—S. O. WAIFE

Imperfect Homeothermia in the Hereditary Obese-Hyperglycemic Sydrome of Mice. T. R. A. Davis and J. Mayer. *Am. J. Physiol.* 177: 222, 1954.

Hereditary obese and hyperglycemic mice are very sensitive to cold. Death often occurs at temperatures easily tolerated by normal animals. The thyroid and adrenal cortex are not concerned. Those made obese by gold-thioglucose are resistant to cold. Also, shivering and piloerection do take place. Thus, three possible causes of failure of thermogenesis are eliminated. Differences in activity were also eliminated, and resistance to high temperatures is normal in obese mice. Hereditary obese-hyperglycemic mice do not increase their oxygen use in response to cold. Fall in body temperature and death result. Thin animals may double their metabolic rate as a result of exposure to cold. The hereditary obese-hyperglycemic mice recovered from exposure to cold provided the central temperature did not fall below 14–16° C.—M. J. OPPENHEIMER

When animals which are hereditarily obese were made to exercise, a greatly decreased weight gain was observed, even though their food intake was increased. Control animals on the same diet and activity maintained their weight. These observations are of great importance, suggesting that genetic factors are of importance in the causation of obesity through alterations in the individual's metabolism as yet unexplained, and that intelligently supervised programs of exercise may yet prove to be important in the control of obesity.

Exercise, Food Intake and Body Weight in Normal Rats and Genetically Obese Adult Mice. J. Mayer, N. B. Marshall, J. J. Vitale, J. H. Christensen, M. B. Mashayekhi, and F. J. Stare. *Am. J. Physiol.* 177: 544, 1954

Short periods of exercise (sedentary) in previously sedentary rats did not increase food intake. Body weight and food intake showed a significant but small decrease. If the exercise was made longer (normal), weight was maintained and food intake increased. When exercise was greatly prolonged (made excessive), weight was lost, food intake decreased, and the animals appeared badly. Sedentary and exhaustion ranges were considered nonresponsive since food intake was not increased. Hereditary obese mice exercised for one hour daily showed a greatly decreased weight gain even though food intake was increased. Under this program, normal mice were unaffected. The importance of considering exercise as well as food intake in problems of obesity is well illustrated.—M. J. OPPENHEIMER

In general, the results obtained in weight reduction through the use of anorexogenic agents has not been impressive. Approximately 25 per cent of the patients so treated appear to be benefited. It is curious that the authors of the following paper observe an occasional gain in weight despite a consistent reduction in appetite in the treatment of obese hypertensive patients.

The Effect of D-Amphetamine Sulphate in the Treatment of the Obese Hypertensive Patient. E. L. Goodman, and E. L. Housel. *Am. J. Med. Sc.* 227: 250, 1954.

The effects of oral and intravenously administered *d*-amphetamine upon the blood pressure, heart rate, and peripheral circulation in obese hypertensive subjects were studied. Fourteen patients took the drug orally over an average period of 152 days without any increase in blood pressure above the fluctuations observed prior to the onset of the study. Although an anorexogenic effect was noted in each instance, changes in body weight were inconstant, varying from a gain of 10 lb. to a loss of 10 lb. Intravenous administration resulted in a slight rise in blood pressure in most instances and a moderate peripheral vasoconstriction, the latter being detected by the use of plethysmography. A decrease in skin temperature was observed in 5 of 13 patients. There were no side effects noted following intravenous administration of the drug. The authors conclude that *d*-amphetamine consistently reduces the appetite but

that weight loss does not occur without dietary restriction.—C. R. SHUMAN

It has been widely conceded that obesity may be a manifestation of a neurotic personality. However, it seems more likely that obesity is the result of a combination of genetic and environmental factors not necessarily related to personality disturbances. Group therapy has been popularized as a means of reducing overweight persons. Success achieved by these measures does not necessarily support the existence of a psychiatric cause for obesity in these patients.

Group Therapy in Reducing. Two-Year Follow-Up of Boston Pilot Study. A. B. Kurlander. *J. Am. Dietet. A.* 29: 337, 1953.

One hundred-twenty persons, mostly women, attended weekly meetings lasting from one to one and one-half hours for 16 weeks—during which time discussions centered around the eating and reducing problems of members. Weights were recorded at the beginning of the sessions, end of the group meetings, 12–18 months after the end, and 24 to 28 months later. At the second-year follow-up current weights were obtained on 95 of the original 120. The desirable weight of each subject was determined according to the Metropolitan Life Insurance Company weight standard. Achievement was measured in terms of excess weight lost and selected into three ranges: persons who lost 100 per cent of excess weight; those who lost 50–100 per cent, and those who lost between 10 and 100 per cent. Of 95 persons who were followed for two years, one person showed a loss of 100 per cent excess weight after one year, but had regained $^2/_3$ of the weight loss during the second year. Eight persons showed a loss of 50–100 per cent excess weight after one ' ar but at the end of two years 4 no longer showed this amount of weight loss. Forty-three persons showed a loss of 10–100 per cent of excess weight after one year but after two years 14 no longer showed this amount of loss.

This study shows that getting together in groups to talk about problems of obesity is not a sure cure for obesity. Though some persons gain will power through groups, they do not possess sufficiently strong motivation to carry on alone. Group methods combined with personal advice will ultimately prove the most successful method of handling overweight persons.—J. SMITH

In the popular magazines of today one finds every month advice given to the reader concerning the virtues of some particular weight-reducing program. Some of these programs have been prepared by preeminent authorities and may be worthwhile if conducted under medical supervision.

The Merry-Go-Round of Reducing Diets. R. M. Leverton. *J. Am. Dietet. A.* 29: 333, 1953.

"In general present-day-reducing diets come from one of four sources: (a) figments of unbridled imaginations, uninhibited by scientific knowledge, (b) accumulations of both sound and 'screw-ball' ideas which happened to produce the desired results for someone at some time, (c) sound scientific ideas leading to a careful and intelligent planning of low-calorie diets, and (d) the same as (c) but with an added feature—organized scientific testing of the diet with a group of overweight people." This statement from a scientifically accurate, popularly written article sets the stage for a set of specifications for effective, constructive, low calorie diets. According to the author, these diets should: (a) supply a caloric intake below the caloric need; (b) improve the nutritional status of the patient if improvement is needed, or maintain an existing high level of good nutrition; (c) develop the patient's taste and interest in eating an assortment of everyday foods which will provide an optimal diet; (d) appeal to the reducer or patient, i.e., appeal to his ambition to reduce, his common sense, his aesthetic sense, or if nothing else, to his sense of martyrdom; and (e) they should be recommended, prescribed, explained, and followed under the direction of a doctor and dietitian who are themselves of normal weight (!).

This article is recommended for interesting, informative reading.—J. SMITH

Diet surveys obtained from obese individuals by the recall or food record methods are notoriously unreliable, as the following survey demonstrates.

Food Intakes of Obese and Non-Obese Women. R. Beaudoin and J. Mayer. *J. Am. Dietet. A.* 29: 29, 1953.

By a study of diet records for 269 women the authors attempt to answer three specific questions: (a) What is the caloric intake of obese women compared to that of subjects of normal weight? (b) Is the distribution of fat, protein, and carbohydrate in the diet of the obese different from that of normal subjects? (c) Are the relative size and the frequency of meals different in obese than in subjects of normal weight? Data were collected concerning: (1) One-day food records of 58 women of normal weight, 59 overweight women, and 45 underweight subjects. (2) Three-day food records from 12 overweight women and 12 women of normal weight, matched for height and weight. (3) Dietary histories of 30 nondiabetic obese women under 60 years of age, and (4) research dietary histories for 20 women of normal weight and 30 obese women ranging in age from 17 to 42 years.

The average daily caloric intake of the three groups of women of normal weight agreed remarkably well—2198, 2196 and 2201 calories respectively. There was

less agreement among the overweights—1964, 1591, 2524, and 2829 calories/day for the four groups above. The higher values from the diet histories taken by careful interview may indicate that the obese women required more careful questioning than the women of normal weight in order to disclose their dietary pattern.

An analysis of the per cent distribution of calories among protein, fat, and carbohydrate showed 12.7–16.4 per cent protein, 36.8–46.08 from fat, and 39.5–49.7 from carbohydrate. This does not agree with the 20 to 25 per cent of fat calories usually suggested for adults. The obese showed no significant deviation in calorie partition from that shown by normal women.

All of the nonobese women reporting by the one-day food record ate breakfast, lunch, and dinner, and a high proportion of them took snacks. The authors questioned the report of the frequency and size of meals of the overweight women using the record method, since the total calorie intake appears too low. One hundred per cent of these reported having noon and evening meals, 98 per cent breakfast, and 33 per cent morning, afternoon, and evening snacks. Obese women contacted through research dietary histories reported more snacks, with 80 per cent having an evening snack.

The authors believe that for obese women the food recording methods give grossly inadequate mean caloric intakes. The research dietary history yielded results in agreement with physiologic considerations.—J. Smith

DIETARY FACTORS IN HYPERTENSION

Sodium restriction in the management of hypertension has been recognized as an important item in France for 50 years. The low salt diet, however, remains a practical—and psychological—problem. It is advised that the protein content of the diet be maintained at a level adequate to meet the patient's requirements—which may not always be achieved by the use of the "rice" diet.

The Role of Minerals in the Dietary Treatment of Hypertension. H. Gounelle. *Méd. et Hygiène* 11 (250): 339, 1953.

The importance of sodium chloride in the diet of hypertensives is today undisputed. The beneficial effects of the salt-free diet were demonstrated in France as early as 1905 by Ambard and Beaujard, and their example has governed the therapy of hypertension in France for 50 years. Their influence, however, was limited to that country. Later (1920–1925), Allen stressed the role of sodium, but was accorded little attention. Not until Kempner (1944) published his results with the rice diet, and after subsequent investigation had revealed that its value resided primarily (if not exclusively) in its restriction of sodium, has sodium restriction been universally accepted.

Although one-third of hypertensives will improve on the Kempner diet, it must be admitted that such a regimen is all but impossible except during hospitalization.

It must also be admitted that sodium depletion is not the whole explanation. In some cases, reduction of blood pressure occurs even on a diet high in salt. In France, during the famine period of 1941–1945, all clinicians observed a lesser elevation of blood pressure and a decrease in the frequency of hypertensive accidents. The current diet was a low energy one (about 1800 calories), very poor in proteins and lipids, and high in carbohydrate. Many of the substitute foods (such as soups) employed freely to satisfy hunger were invariably highly salted. Despite this "inundation" with water and salt, hypotension was the rule.

The evidence leads the author to recommend the following therapeutic plan: strict rice diet in a hospital for 3–4 weeks; when signs of functional improvement appear, augmentation of the diet by a vegetarian diet (seasoned but not salted) low in calories (1800–2000). In case of excessive weight loss or of protein- or sodium-deficiency anemia, supplementation for 3 to 4 days by meat, fish, or (weighed) salt. The "hypertensive diet," then, is understood by this author to be a strictly salt-free one, interrupted for brief intervals by measured amounts of salt; low in calories; composed principally of carbohydrate; containing just enough protein to meet the minimum nitrogen requirement; and practically fat-free.—C.-J. Howell

Practical Results of the Dietary Treatment of Hypertension. F. Vivanco. *Méd. et Hygiène* 11 (250): 340, 1953.

The author justly observes that treating hypertension and treating hypertensives are two different matters. In the latter case, dietary treatment has as its object the avoidance of sudden variations in blood pressure produced by excesses of various kinds, and the prevention of complications.

There is no doubt that the Kempner rice diet decreases blood pressure. Experience with this regimen in Madrid has consistently demonstrated reduced pressure when the diet is followed for more than 2 weeks; however, the patients' general condition is not always improved. Circulatory improvement is no greater than with other low salt diets. The rice diet is, moreover, "anti-physiologic" and does not meet the individual's daily requirements. Since its virtues are no greater than those of any salt-poor regimen, the author concludes that it should not be employed for long periods. It inevitably produces great loss of weight; often leads to negative nitrogen balance; and never pleases the patient.

Furthermore, its use is dangerous in cases of hypertension accompanied by chronic renal insufficiency.

Other, better-balanced low sodium diets must be preferred, and various regimens meeting these requirements are now being tested in many countries. Their value in hypertension depends on the ability and willingness of the patient to adhere strictly to a dietetic prescription.

Agreement seems unanimous on the necessity for caloric restriction in the case of the obese hypertensive, since the correlation between obesity and hypertension is universally recognized. Anything which can be done to reduce weight can be considered as prophylactic or palliative dietary treatment of hypertension.

As for dietary factors other than sodium (and calories), lipids and proteins are without influence on hypertension. However, where hypertension is complicated by marked renal insufficiency, in the author's opinion, it is well to reduce dietary protein to the physiologic minimum (50 Gm.). Fat is important only as it affects the caloric level.—C.-J. HOWELL

Effects of Withdrawal and Restoration of Dietary Sodium Chloride upon Urinary Electrolytes in Patients with Hypertension. F. T. Hatch. *Metabolism* 3: 160, 1954.

Patients with severe hypertensive disease were studied from the standpoint of effect of the abrupt withdrawal and subsequent restoration of salt to the diet upon the urinary electrolyte excretion pattern. For 3 weeks following a marked salt restriction diet there was a gradual decline in the daily output of sodium and chloride. Despite these losses, there was maintenance of essentially normal electrolyte levels; however, there was an overall decrease in the total body content of sodium and chloride balances.

It was interesting to note that upon partial restoration of salt the added chloride soon reappeared in the urine. However, none of the added sodium ion was excreted in the urine for at least four weeks. One hypothesis offered to account for this is the movement of sodium into bone where it is presumably associated with other anions than chloride.—C. R. SHUMAN

Protein restriction appears to be necessary only when renal insufficiency and azotemia are present. There is little evidence that the lipid content of the diet per se is of significance in the dietary management of hypertension, although it may be important to restrict dietary fat if atherosclerosis is present.

The Role of Proteins in the Dietary Treatment of Hypertension. J. Delfosse, P. Osinski, and F. Stein. *Méd. et Hygiène* 11 (250): 340, 1953.

Experimental data on the effect of protein on renal mechanisms and on the development of hypertension have revealed significant species differences. A high protein diet, which seems to increase blood pressure in the rat, has no similar effect in the dog or in man.

Although a high protein diet does not increase blood pressure in the normal man, nor produce serious renal lesions, the same diet may aggravate the condition when there is a diseased kidney or hypertension of renal origin.

The role of the hormones is surely important in the regulation of arterial tension. A high protein diet facilitates ACTH production and hypertrophy of the adrenal cortex in rats exposed to various stimulants. Clinically, hypertension has been known to occur on diets containing no animal protein—probably due in part to hyperfunction of the adrenal cortex.

The influence of certain amino acids, such as glutamic acid, on the nervous system and the carotid sinus is well known, but no correlation between experimental and clinical observations has been established to date.

On the available evidence, it would seem that the role of dietary protein is minimal in the treatment of hypertension. Protein restriction in hypertension of renal origin is justified. In hypertension of humoral origin—even should certain amino acids contribute to the synthesis of hypertensive substances—the influence of dietary protein is surely very slight. Where hypertension is of nervous or hereditary origin, protein restriction is useless.—C.-J. HOWELL

Lipids in the Dietary Treatment of Hypertension. M. Coppo and G. P. Vecchi. *Méd. et Hygiène* 11 (250): 339, 1953.

Several factors are involved in any consideration of the role of lipids in hypertension: the quality, as well as the quantity of the fat in the diet; the protein content of the regimen; and the quality of the amino acids furnished.

Researchers in Modena have been studying the consequences of an eventual excess of dietary fat on the lipid content and lipoprotein structures of the plasma. Hyperlipemia, the definite and permanent increase of total blood lipids or of its fractions, can occur through the collaboration of familial, constitutional, or dietary factors. However, the authors regard the exogenous contribution of fat as essential for permanent hyperlipemia.

Clinical signs of hyperlipemia are numerous and diverse. In the authors' experience, hyperlipemia and hypercholesteremia are associated with suggestive frequency with cutaneous or corneal lesions of xanthomatous origin. In men, hyperlipemia is more commonly accompanied by arcus corneae and by coronary or peripheral atherosclerotic lesions; in

women, on the other hand, the most frequent signs are xanthelesma and hepatobiliary changes.

The role of the lipids, cholesterol, and diet in the pathogenesis of atherosclerosis is generally accepted; opinion differs only on their mode of action. The authors approve a definite and permanent reduction of dietary fat and the total exclusion, as far as this is possible, of animal fat and particularly of cholesterol.—C.-J. Howell

ASCORBIC ACID

By means of carbon-labeled substances it has been possible to demonstrate that ascorbic acid is endogenously synthesized from glucuronic acid. Previous work has demonstrated that glucuronic acid is produced in the body from glucose through an alternative pathway observed in carbohydrate metabolism. While these observations are of great interest, there is no indication that a sufficient production of vitamin C can be achieved through this route to satisfy metabolic requirements.

Glucuronic Acid as a Precursor of Ascorbic Acid in the Albino Rat. H. H. Horowitz and C. G. King. *J. Biol. Chem.* 205: 815, 1953.

Male albino rats were stimulated with Chloretone until their daily ascorbic acid excretion exceeded 30 mg. per day. Uniformly labeled glucuronolactone-C^{14} was injected into these rats and the ascorbic acid excreted in the urine was analyzed for C^{14} content and distribution. The conversion of the glucuronolactone to C^{14}-ascorbic acid in the albino rat was demonstrated. The yield of C^{14}-ascorbic acid was 4 to 8 times greater than that obtained from glucose in similar experiments, thus demonstrating a sequence of steps from D-glucose to L-ascorbic acid via an intermediate synthesis of D-glucuronic acid.—M. K. Horwitt

Intensive studies dealing with vitamin C have created more problems with respect to its biochemical actions than they have solved. This is particularly true with reference to its action in the metabolism of the supporting tissues of the body.

Unknowns in Vitamin C. L. T. Harris. *Pub. Health Rep.* 69: 429, 1954.

Vitamin C requirements, distribution, and mode of action are three subjects which need further clarification. Differences of opinion exist as to the daily requirement of this vitamin. Considerably more than the scurvy-preventing dose is required in the guinea pig for optimal growth. There is no way of proving that man, too, is better off with doses greater than that needed to prevent scurvy. A test is needed for detection of minor degrees of vitamin C deficiency.

The distribution of vitamin C is puzzling. Some fruits, plants, and animal tissues are rich in this substance, while others have none. Information as to the mechanism by which this vitamin acts might be obtained if the reason for its distribution were known.

Vitamin C is known to have a reducing activity. A deficiency of the vitamin results in a decreased formation of tissue such as dentine, enamel, cement, bone, and collagen. The vitamin has a role in the conversion of folic acid to folinic acid and the metabolism of tyrosine. There may be a relation between adrenal function and vitamin C. Though these things are known, it is impossible to relate vitamin C with any enzyme system, as can be done with many of the B vitamins.—M. W. Bates

Contrary to previous reports, which had indicated a sparing action of ascorbic acid for the corticosteroids, the following report indicates that ascorbic acid depresses corticosteroid secretion and favors the production of the salt-active steroids.

Effect of Ascorbic Acid on Insulin Sensitivity in the Rat. N. Allegretti, and G. Vukadinovic. *Am. J. Physiol.* 177: 264, 1954.

Ascorbic acid does not change the blood sugar level in normal or demedullated rats. This is interpreted to mean that it has no effect upon the activity of endogenous insulin. However, if ascorbic acid is given to normal or demedullated rats which have previously been injected with insulin, a greater degree of hypoglycemia results. This indicates a greater sensitivity to injected insulin. The authors conclude that ascorbic acid depresses secretion of C-11 oxygenated corticosteroids. This is brought about by shifting the secretion to corticoids concerned with the metabolism of electrolytes. This theory would be confirmed if sodium could be shown to increase the hypoglycemic effect of insulin and potassium to decrease it. Ascorbic acid has a DCA-like effect.—M. J. Oppenheimer

In the previous paper, ascorbic acid given to normal rats increased the responsiveness to insulin, while in the following paper insulin tolerance curves revealed a progressive resistance to hypoglycemia during ascorbic acid deficiency.

Carbohydrate Metabolism in Ascorbic Acid Deficiency. H. Bacchus, and M. H. Heiffer. *Am. J. Physiol.* 176: 262, 1954.

Disturbed carbohydrate metabolism was studied during ascorbic acid deficiency in guinea pigs. Insulin tolerance curves indicate a progressively developing resistance to hypoglycemia during ascorbic acid lack. The result is the same even if the adrenals are removed. Glycogenesis is disturbed in ascorbic acid deficiency according to data from this work. It is

suggested that there is probably no decreased insulin secretion nor adrenal hyperactivity in the disturbances of carbohydrate metabolism.—M. J. OPPENHEIMER

With results comparable to those observed in experimental animals, upon which a bioassay method for ACTH is based, the authors have observed a fall in adrenal ascorbic acid content following the administration of ACTH in the human.

Concentration of Ascorbic Acid in Human Adrenal Cortex Before and After ACTH Administration. F. J. Agate, Jr., P. B. Hudson, and M. Podberezec. *Proc. Soc. Exper. Biol. & Med.* 84: 109, 1953.

Adrenalectomy was carried out in patients with metastatic cancer and the ascorbic acid content of the adrenals determined before and after ACTH treatment. The pretreatment level was found to be 131 ± 8 mg./100 Gm. of tissue in the male and 139 ± 5 mg. in the female. A 32 per cent depletion was noted 2 to 3 hours after the intravenous injection of 25 U.S.P. units of ACTH. This dose is 7 to 8 times that required per kilogram of body weight for the male hypophysectomized rat.—L. W. KINSELL

Increased oxaluria following the administration of ascorbic acid has been observed in humans, as it has previously in experimental animals.

Urinary Oxalate Excretion by Man Following Ascorbic Acid Ingestion. M. P. Lamden and G. A. Chrystowski. *Proc. Soc. Exper. Biol. & Med.* 85: 190, 1954.

Oxalic acid has previously been shown to be a product of the *in vitro* oxidation of ascorbic acid. Increased ascorbic acid ingestion in guinea pigs results in increased urinary oxalate, and one of the end products of the metabolism of radioactive 1-C^{14}-L-ascorbic acid is urinary oxalate.

In the present study, mean oxalate excretion in normal males on an average diet was found to average 38.3 mg. per 24 hours. The daily ingestion of more than four grams of ascorbic acid resulted in increased urinary excretion of oxalic acid. Lesser amounts than this produced no significant change.—L. W. KINSELL

VITAMIN D

The interesting observations of Zellerström upon the action of vitamin D in increasing alkaline phosphatase activity within the tissues may receive some support in the observations made by the authors of the following paper.

Observations on the Metabolic Effects of Vitamin D in Fanconi's Syndrome. R. M. Salassa, M. H. Power, J. A. Ulrich, and A. B. Hayles. *Proc. Staff Meet., Mayo Clin.* 29: 214, 1954.

Fanconi's Syndrome is the name applied to a situation in which the renal tubules are abnormal but the glomerular function is relatively normal. The characteristics are a high renal clearance of phosphate associated with low serum inorganic phosphate, and rickets or osteomalacia. There is also a high renal clearance of glucose with glycosuria but a normal glucose tolerance response. The renal excretion of amino acids and ammonia is increased and there is a hyperchloremic acidosis with normal serum calcium and blood urea.

In two cases of this syndrome studied at the Mayo Clinic, large doses of vitamin D, 400,000 units daily, modified the hypophosphatemia, the glycosuria, amino-aciduria, and hyperchloremic acidosis. The vitamin also favorably influenced the high renal clearance of phosphate. The pain and weakness of the legs were relieved and the patients regained their ability to walk without support.

Although a longer follow-up period is necessary before final evaluation, these studies suggest that vitamin D may be therapeutically valuable in Fanconi's Syndrome.—S. O. WAIFE

Zellerström and his co-workers have demonstrated that vitamin D activates alkaline phosphatases in kidneys, intestines, and bones. Vitamin D administered to patients with the Fanconi syndrome reduced the high renal clearance of phosphate and the glycosuria. The possibility that renal tubular resorption of glucose depends upon tubular phosphatase has been suggested by Drabkin. These observations may explain to some extent why vitamin D was effective in the treatment of the Fanconi syndrome.

It has also been suggested that vitamin D may be implicated in carbohydrate metabolism by activating the respiratory enzyme complexes of the mitochondria which catalyze the reactions of the citric acid cycle. In the following paper it was observed that the highest citrate values in tissues were found to be induced by vitamin D administration.

Vitamin D and Tissue Citrate. H. Steenbock and S. A. Bellin. *J. Biol. Chem.* 205: 985, 1953.

These experiments were designed to study the increased elimination of urinary citrate which is affected by the administration of vitamin D. Rats were placed on normal and rachitogenic diets with and without sodium bicarbonate, and the blood, heart, kidneys, small intestines, liver and bone tissues were examined for the effect of vitamin D on citrate content. As had been proved with urinary citrate, increases in tissue citrate were produced with rats on either normal or rachitogenic rations. The highest citrate values were obtained with a low phosphorus intake, but the greatest increase, induced by vitamin D, was found with rations adequately supplied with phosphorus. The sodium bicarbonate induced alkalosis, which is

known to increase urinary citrate; it had little or no effect on the level of blood citrate. It was therefore evident that the effect of vitamin D on blood citrate was not mediated through an increased systemic alkalinity, although vitamin D has been shown to increase the alkalinity of the urine of rachitic rats. The liver was the only tissue studied in which the citrate content was not increased by physiological doses of vitamin D. Apparently the liver can catabolize large amounts of citrate. It appears that the increase in urinary citrate is a reflection of its increased accumulation in certain tissues.—M. K. HORWITT

It is interesting to note that rickets was demonstrated in a group of premature children who received vitamin D. One possibility which might explain this enigmatic finding is that rickets is most easily induced when the growth rate is rapid.

The Relationship of Vitamin D Administration to the Prevalence of Rickets Observed at Autopsy During the First Two Years of Life. R. H. Follis, E. A. Park, Jr., and D. Jackson. *Bull. Johns Hopkins Hosp.* 92: 426, 1953.

These authors previously showed the high incidence of rickets of moderate or severe degree in children from about the age of two months to two years as determined from autopsy studies. In this group there were 147 full-term children with a definite history of never having received vitamin D throughout their entire life. Rickets was present in 69 per cent of this group. In three-fourths of the group with rickets the disease was moderate or severe. There was no relationship between the duration of terminal illness and the presence or absence of rickets. It is interesting that since growth is necessary for rickets to manifest itself there was evidence of "growth suppression" in one-third of the cases having no, or only slight, evidence of rickets.

Among children, both full-term and premature, who had received vitamin D for varying periods before death, a great variation in the severity of rickets was found. In a group of premature children who received known quantities of vitamin D, rickets of a moderate or severe degree was present in a high proportion of cases. The authors presented the concept that rickets is "normally" present in the premature ingesting a maximal quantity of milk and as much as 6000 units of vitamin D daily. This could be explained by the rapid production of cartilage of bone matrix which outstripped the ability of inorganic salts to be deposited. As the authors note, there are many variables which prevent the stating of a definite conclusion as to the levels of vitamin D administration which will insure the absence of rachitic changes in the skeleton of the full-term child. However, in a hospital population of sick children, from 400 to 800 units of vitamin D a day would not always appear to protect full-term infants under one year of age.—S. O. WAIFE

Vitamin D and Intestinal Phytase. H. Steenbock, C. H. Krieger, W. G. Wiest, and V. J. Pileggi. *J. Biol. Chem.* 205: 993, 1953.

In 1929, Steenbock and his collaborators revealed that cereal phosphate did not always have the same nutritive value as inorganic phosphate. This report was followed by many investigations which confirmed the relative nonavailability of phytic acid phosphate, unless the phytic acid was previously hydrolyzed or fed simultaneously with vitamin D. In 1936, Lowe and Steenbock recognized that hydrolysis *in vivo* by an intestinal phytase might be responsible for the improvement effected when diets were supplemented with vitamin D. The present paper reviews the history and controversy regarding phytic acid phosphate availability and reports the present position of the Steenbock laboratory on this subject.

Chicks on a rachitogenic diet had average intestinal phytase contents of 2.5 units per Gm. of wet tissue. The addition of vitamin D to this diet produced chicks with tissue levels which averaged approximately 4.3 phytase units. Similar results were obtained with rats with and without vitamin D in their rations. The reaction causing the increase in the extractable intestinal phytase effected by vitamin D on rats and chicks kept on cereal rachitogenic diets was apparently not limited to cereal rations or to the rachitic state. Similar observations were made with rats kept on noncereal rations which furnished either optimal or excessive amounts of phosphorus and optimal amounts of calcium. There was no evident relationship between the severity of rickets and phytase activity.—M. K. HORWITT

EXPERIMENTAL STUDIES ON CHOLESTEROL

Heparin has previously been demonstrated to have anti-chylomicronemic effect and lipemia-clearing effect when injected into human subjects. It is now further shown that in patients with hypercholesterolemia the serum cholesterol and phospholipid values are decreased and the electrophoretic pattern of the serum lipids is altered following heparin administration. There appears to be a reduction of the β-globulin lipid peak and an increase in α-globulin which may be the result of the influence of heparin upon the protein-lipid binding of cholesterol and phospholipid.

The Effects of Injected Heparin on the Electrophoresis of the Lipoproteins in Patients with Hypercholesterolemia. R. E. Bolinger, H. J. Grady, and C. J. Slinker. *Am. J. Med. Sc.* 227: 193, 1954.

Paper electrophoresis was employed to examine the effect of heparin upon the cholesterol and phospholipid patterns in patients with hypercholesterolemia.

Serum was obtained before and after the injection of heparin from 4 patients with elevated blood cholesterol and 1 normal subject. In the patient group, the serum cholesterol and phospholipid values decreased. In each instance the electrophoretic pattern of the lipids following heparin revealed a blunting of the β-globulin lipid peaks with a shift of the peaks toward the alpha region and an increase in the α-globulin lipid peaks. In 2 of the patients the cholesterol levels as obtained by integration from the paper strips decreased, and in the other 2 patients the values increased. In the case of phospholipid, the values found from the paper strips were increased after heparin. In the hypercholesterolemic cases, the change observed was a decrease in the serum lipids and an increase of these substances in the protein-bound phase, with changes appearing in the lipoprotein mobilities after heparin. Heparin may influence the protein-lipid binding of cholesterol and phospholipid.—C. R. SHUMAN

Hypercholesterolemia produced in dogs by dietary means did not appear to be influenced by sulfur amino acid deficiency in the dietary intake of these animals.

Response of Dogs to Cholesterol Feeding. K. H. Shull, G. V. Mann, S. B. Andrus, and F. J. Stare. *Am. J. Physiol.* 176: 475, 1954.

Diets were used to induce hypercholesteremia in dogs. Although the intake of cholesterol was constant, serum cholesterol levels showed fluctuations. Dogs were variable in response to intake. No evidence was found to indicate that sulfur amino acid deficient alpha-protein diets produced a greater rise in serum cholesterol than similar diets including methionine or casein. Monkeys behave differently on similar dietetic regimes. Lipoproteins and S_f 12–20 molecules were increased in the diet-fed animals. No atherosclerosis was found, although a hypercholesteremia and hyperlipoproteinemia were maintained in some rats for 11–22 weeks.—M. J. OPPENHEIMER

Influence of Sulfur Amino Acid Deficiency on Cholesterol Metabolism. L. C. Fillios, and G. V. Mann. *Metabolism* 3: 16, 1954.

The effect of diets made with soybean protein low in sulfur-containing amino acids was studied with respect to cholesterolemia in animals. It was observed that the substitution of these diets for casein was associated with hypercholesterolemia. However, supplementation of the soybean protein diet with *dl*-methionine partially prevented the increased hypercholesterolemia. Impairment of appetite and growth was observed in adult rats fed the soybean protein diets without cholesterol; supplemental methionine did not correct this condition. Analysis of liver tissue for cholesterol revealed poor correlation between this and serum cholesterol in the hypercholesterolemic animals. No evidence of atherosclerosis was observed in these relatively short-term experiments.—C. R. SHUMAN

The main pathway for disposal of cholesterol is that of intestinal excretion in the form of coprosterol and dihydrocholesterol. The intestinal sites of absorption and excretion have been studied in the following paper.

Observations Concerning the Production and Excretion of Cholesterol in Mammals. XI. The Intestinal Site of Absorption and Excretion of Cholesterol. S. O. Byers, M. Friedman, and B. Gunning. *Am. J. Physiol.* 175: 375, 1953.

In these experiments the small intestine was responsible for most of the cholesterol excreted into intestinal contents. Exogenous cholesterol could be absorbed only in the caudal half of the small bowel. —M. J. OPPENHEIMER

Observations Concerning the Production and Excretion of Cholesterol in Mammals. XII. Demonstration of the Essential Role of the Hepatic Reticulo-Endothelial Cell (Kupffer Cell) in the Normal Disposition of Exogenously Derived Cholesterol. M. Friedman, S. O. Byers, and R. H. Rosenman. *Am. J. Physiol.* 177: 77, 1954.

Six hours after oral cholesterol this material was found in the Kupffer cells of the liver. After 24 hours the amount in the reticuloendothelial cells was increased and some was to be found in liver cells. Reticuloendothelial blockade reduced the amount of cholesterol deposited in the liver after oral ingestion. Under these same circumstances chylomicra persisted in peripheral blood and there was a hypercholesteremia. The conclusion is drawn that hepatic reticuloendothelial cells play a role in the deposition of exogenous cholesterol.—M. J. OPPENHEIMER

Reports from countries where the incidence of degenerative heart disease is much lower than in the United States offer increasing evidence of the interrelationships between dietary fat, serum cholesterol, and atherosclerosis. The following paper presents data on serum cholesterol concentrations in Spanish adults at various ages; the contrast between the two economic groups investigated is significant.

Studies on the Diet, Body Fatness and Serum Cholesterol in Madrid, Spain. A. Keys, F. Vivanco, J. L. R. Miñon, M. H. Keys, and H. C. Mendoza. *Metabolism* 3: 195, 1954.

An extensive study was conducted by the authors of the bodily dimensions and serum cholesterol concentrations of 181 clinically healthy adults in Madrid comprising men of the professional class and men and women in a poor sector (Vallecas) of the city. The

diets of the professional class corresponded closely to American diets in caloric and fat content. The diets of the Vallecas families were low in caloric and fat content. The latter individuals were shorter and much thinner than those of the professsional class. The younger Vallecas women were unusually thin, while the older women were comparable to American standards for relative body weight. The serum cholesterol values in the professional men conformed to American norms and showed a steady rise with age from 20 to 50 years. Serum cholesterol values in younger Vallecas men were similar to those of the professional class, but with advancing age the cholesterol values tend to decline rather than rise. Estimation of subcutaneous fatness and body weight could not account for cholesterol differences in the males of these two classes. It is believed that total dietary fat is the main determinant of serum cholesterol in men above the twenties and that total caloric intake is important only at levels of gross undernutrition. Degenerative heart disease is much less common among Spanish males than among Americans. The major factor in this difference lies in the relationship among dietary fats, serum cholesterol, and atherosclerosis.—C. R. SHUMAN

In the human, elevated cholesterol values are frequently found in conjunction with obesity. A similar finding is recorded in hereditarily obese mice.

Hypercholesteremia in the Hereditary Obese-Hyperglycemic Syndrome of Mice. J. Mayer, and A. K. Jones. *Am. J. Physiol.* 175: 339, 1953.

When hereditary obese hyperglycemic mice are 4–5 months old the serum cholesterol is twice that of nonobese control littermates. An elevated serum cholesterol is a definite part of the syndrome. A further increase in serum cholesterol was produced by high protein and high carbohydrate diets lasting for a 2-week period, also by fasting and by growth hormone. The serum level was decreased by thyroxine. Although ACTH and growth hormone increase the level in nonobese mice, it is decreased by the two types of diets previously mentioned and by thyroxine. —M. J. OPPENHEIMER

The relationship between cholic acid and cholesterol has been of interest, since observations have shown that they appear to be directly related in their serum concentrations. It appears from the following work that in the formation of cholic acid from acetate, cholesterol is one of the intermediate stages.

The Conversion of Cholesterol and Acetate to Cholic Acid. I. Zabin, and W. F. Barker. *J. Biol. Chem.* 205: 633, 1953.

Two Gm. of labeled cholesterol prepared biosynthetically was injected intravenously over a 3-day period, into a 10-kilo male dog which had a biliary fistula and a duodenostomy. Bile could thus be collected and readministered. The activity found in the carboxyl carbon in the cholic acid isolated from bile proved that cholesterol was converted into cholic acid by removal of no more than 3 carbon atoms, carbons 25, 26, and 27. Formation of cholic acid from acetate by a pathway which does not involve the formation of cholesterol might be expected to produce a cholic acid with a different pattern of isotope distribution than that obtained from cholesterol. To test this hypothesis, methyl-labeled acetate was injected into the animal, and the samples of cholic acid were obtained and analyzed. The pattern of isotope distribution obtained when methyl-labeled acetate was used as a direct labeled precursor was identical to that obtained when labeled cholesterol was used. These experiments confirm the assumption that cholesterol is an obligatory intermediate in the formation of cholic acid from acetate.—M. K. HORWITT

Role of Cholate in Dietary-Induced Hypercholesteremia of Rats and Rabbits. R. H. Rosenman, S. O. Byers, and M. Friedman. *Am. J. Physiol* 175: 307, 1953.

When rats are fed cholesterol and cholate at the same time there is marked chronic hypercholesteremia. However, there is no atherosclerosis. Plasma cholate levels seem unrelated to the hypercholesteremia.—M. J. OPPENHEIMER

CARBOHYDRATE METABOLISM

The utilization of glucose by the cells depends upon the presence of insulin, which according to present concepts increases the permeability of the cell membrane to glucose and certain other sugars of similar molecular configuration. This action of insulin is apparently responsible for the results observed in the following paper.

Glucose Pool and Glucose Space in the Normal and Diabetic Dog. G. L. Searle, E. H. Strisower, and I. L. Chaikoff. *Am. J. Physiol.* 176: 190, 1954.

The authors used a single injection and constant infusion method with labeled glucose to determine the miscible glucose pool. In diabetes this pool is three times greater than in controls. Insulin restores it to control values. The space occupied by diffusible glucose is approximately 30 per cent of body weight in normal, diabetic, and insulin-treated diabetic dogs. —M. J. OPPENHEIMER

The uptake of glucose by the rat diaphragm has been shown to be antagonized by a lipoprotein substance found in the serum of diabetic animals. The inhibition of glucose uptake in the tissues of diabetic animals was reversible upon the addition of insulin.

It is of interest that the inhibitory lipoprotein fraction was isolated from the blood of a human subjected to insulin-induced hypoglycemia. The production of this inhibitor is apparently related to the anti-insulin activity of the anterior pituitary and adrenal cortex secretions. Further observations of these phenomena in human diabetics are eagerly awaited.

Inhibition of Glucose Uptake by the Serum of Diabetic Rats. J. Bornstein, and C. R. Park. *J. Biol. Chem.* 205: 503, 1953.

Previous studies of an anterior pituitary factor which inhibits glucose uptake by the isolated rat diaphragm may be summarized as follows. First, in alloxan-diabetic rats glucose uptake by the diaphragm is inhibited, and this inhibition is relieved by insulin, by adrenalectomy, and by hypophysectomy. Second, in hypophysectomized rats glucose uptake by the diaphragm is accelerated and can be restored to normal by the injection of pituitary extracts or purified growth hormone in microgram quantities. Third, the inhibitory effect of pituitary fractions and growth hormone is enhanced by concomitant administration of adrenal steroids which are by themselves inactive.

It has been postulated that the growth hormone acts by way of an intermediate substance which may be the true physiological inhibitor of glucose uptake. It seems probable that this inhibitory substance is present in the serum under appropriate conditions. Using hemidiaphragms from normal rats, diabetic adrenalectomized, and diabetic hypophysectomized rats, and incubating them in buffer or 3 per cent albumin, or in serum of variously treated animals, the following results were obtained. Serum from alloxan-diabetic rats inhibits the uptake of glucose *in vitro* by the diaphragm of normal fasted rats. This inhibitory effect is reversed by insulin *in vitro*. Serum from diabetic rats which have been adrenalectomized, or hypophysectomized does not inhibit glucose uptake. The injection of both growth hormone and cortisone into diabetic hypophysectomized rats restores the inhibitory property of the serum. The injection of either substance alone does not restore inhibition and the addition to the serum *in vitro* of the substance not injected is also ineffective. Growth hormone and cortisone added simultaneously to the serum have no effect on glucose uptake. It is concluded that the insulin reversible inhibitor of glucose uptake in the blood of diabetic rats is formed as a result of endogenous pituitary and adrenal cortical activity.—M. K. Horwitt

Insulin-Reversible Inhibition of Glucose Utilization by Serum Lipoprotein Fraction. J. Bornstein. *J. Biol. Chem.* 205: 513, 1953.

As a first attempt in the purification of the serum inhibitor of glucose uptake by rat diaphragm, lipoprotein fractions from rat and human blood were tested for their ability to inhibit glucose uptake by diaphragm. Two methods of obtaining serum lipoprotein were employed, one being similar to the flotation method described by Gofman and the other the fractionation method developed by Cohn and collaborators. Addition of lipoprotein obtained from serum of normal rats had no effect on glucose uptake, while lipoprotein from diabetic serum produced an inhibition which was reversed by addition of insulin. The inhibitor was associated with β_1-lipoprotein fraction and was inactivated by freezing or by standing in an ice bath. The serum of diabetic rats after removal of the lipoproteins by flotation was not inhibitory. No inhibitory lipoprotein fraction was found either in normal human serum or serum from hypophysectomized diabetic rats, but an inhibitory lipoprotein fraction was obtained from the blood of a human subject during hypoglycemia induced by the injection of a large dose of insulin.

In the case of liver slices, an effect on glucose uptake cannot be demonstrated directly, because in liver slices *in vitro*, glucose formation from glycogen exceeds uptake. However, the rate of glutathione synthesis may be regarded as an indicator system for the rate of glucose uptake. Lipoprotein obtained from diabetic serum caused a marked decrease in the rate of glutathione synthesis in liver slices from normal fasted rats as measured by the incorporation of C^{14}-labeled glycine into glutathione isolated as the cuprous salt. This inhibition was partially insulin-reversible. —M. K. Horwitt

SALTS AND WATER

Effect of Increasing Cortisone Dosage on Serum Electrolytes, Plasma Volume and Arterial Pressure of Adrenalectomized Dogs. W. W. Swingle, G. Barlow, E. J. Fedor, M. Ben, R. Maxwell, E. Collins, and C. Baker. *Am. J. Physiol.* 173: 4, 1953.

When adrenalectomized dogs are fed a diet low in sodium they require at least 1.86 mg./Kg./day of cortisone to keep them in good condition with a fairly normal electrolyte pattern. If the serum sodium is low because of inadequate therapy, 1.86 mg./Kg./day will not restore it to normal. Distortion of the electrolyte pattern requires 3.72 mg./Kg./day to restore it to normal. However, if this dose is long continued, overdose effects resembling those of DOCA may result. Although 10 mg./Kg./day for as long as 47 days elevates serum Na and Cl, the effect on K is small. During this regime blood pressure increases. Results on plasma volume were scattered. Large doses of cortisone increase the low values for hemoglobin, hematocrit, and red cell count in chronically adrenalectomized dogs maintained on DOCA.—M. J. Oppenheimer

Effect of NaCl Depletion on Renal Function and Pressor Response to Arterenol in the Dog. G. W.

Tank, and R. C. Herrin. *Am. J. Physiol.* 173: 103, 1953.

Creatinine and para-amino-hippurate clearances were increased during salt depletion. From their data the authors concluded the tubular reabsorption of Na and Cl was not always constant per unit volume of glomerular filtrate. Hypertonic saline infusion depressed filtration rate during depletion but increased filtration rate in normal controls. During depletion, water diuresis was decreased. Depletion decreased the response to arterenol.—M. J. OPPENHEIMER

Effect of Sodium Chloride Upon the Blood Pressure of Normal Dogs When Administered During Dietary Stress. C. M. Wilhelmj, V. W. Meyers, D. P Milani, and H. H. McCarthy. *Am. J. Physiol.* 176: 86, 1954.

Dogs which had been fasted for a long time were fed a high carbohydrate diet. This is considered to be a severe dietary stress and results in a marked systolic hypertension. If salt was added later, there was no significant change in blood pressure. When salt was given with the diet, two of three dogs had a systolic hypertension and one a diastolic rise. The systolic elevation in this latter case (simultaneous salt and high carbohydrate diet) was the same as that obtained when salt was added to the diet of fed dogs. Only the sustained systolic elevation during salt feeding and absence of a sudden fall when salt was stopped are attributed by the authors to the preliminary fasting and high carbohydrate diet. Isocaloric horse meat diets lowered hypertensive levels established previously due to carbohydrate feeding. Salt did not affect this result.—M. J. OPPENHEIMER

Renal Hemodynamic Function, Electrolyte Metabolism and Water Exchange in Adrenalectomized-Hypophysectomized Dogs. J. O. Davis, D. S. Howell, G. L. Laqueur, adn E. C. Peirce, II. *Am. J. Physiol.* 176: 411, 1954.

When either hypophysectomy or thyroidectomy is performed in adrenalectomized dogs there is a decrease in kidney function. As a result of this observation it may be concluded that the change in kidney circulation in the hypophysectomized animal is not due to loss of ACTH alone. The glomerular filtration rate and renal plasma flow was increased by thyrotropin or growth hormone in dogs deprived of adrenal and pituitary. Loss of thyrotropin and growth hormone may explain decreased kidney function after removal of pituitary in previously adrenalectomized dogs. It was possible to support adrenalectomized-hypophysectomized dogs without the use of hormones by use of a high Na diet. DOCA or cortisone would also maintain them. Removal of the pituitary in adrenalectomized dogs produced a diabetes insipidus of short duration. Elevated glomerular filtration rate was well correlated with increased water exchange during use of growth hormone and thyrotropin.—M. J. OPPENHEIMER

Apresoline (l-hydrazinophthalazine) in the Experimental "Eclampsia-Like" Syndrome and Related Aspects of Water Metabolism. A. A. Renzi, and R. Gaunt. *Am. J. Physiol.* 175: 313, 1953.

Unilaterally nephrectomized rats were given a high salt diet and DOCA. When renin was added edema, kidney damage, and death resulted. These findings bear some resemblance to toxemia of pregnancy. If *l*-hydrazinophthalazine (apresoline) were given with the renin, the rats did not die and most of the aspects of the syndrome were prevented. Under the conditions of these experiments, both renin and DOCA caused diuresis (in presence of apresoline) such that daily urine volumes exceeded body weight. Apresoline alone (in doses used here) decreased salt and water excretion in normal rats. Rats treated with apresoline were more susceptible to water intoxication. If apresoline were used in normal rats in doses which did not produce hypotension, there was no effect on water and salt excretion.—M. J. OPPENHEIMER

Effect of Hydration and Dehydration on Hypertension in the Chronic Bilaterally Nephrectomized Dog. C. R. Houck. *Am. J. Physiol.* 176: 183 1954.

After bilateral nephrectomy dogs were maintained on a low salt diet by intermittent peritoneal dialysis. In the absence of dehydration there was hypertension if weight and extracellular fluid volume increased. When there was dehydration and no increase in extracellular fluid hypertension did not develop. Dehydration of hypertensive animals caused some reduction in blood pressure but not to normal. Severe dehydration produced hypotensive shock. Rehydration restored blood pressure to hypertensive levels. These experiments suggest a causal relationship between increased body fluids and hypertension. It is not necessary to maintain the increased body fluids to maintain the hypertension.—M. J. OPPENHEIMER

Effect of Varying Dietary Potassium Upon the Blood Pressure of Hypertensive Rats. R. H. Rosenman, S. C. Freed, S. St. George, and M. K. Smith. *Am. J. Physiol.* 175: 386, 1953.

When dietary intake of potassium is severely restricted the blood pressure in hypertensive rats is reduced markedly. This confirms earlier work. When restrictions were less marked the hypotensive effect was also less.—M. J. OPPENHEIMER

Effect of Cortisone on Blood Pressure of Hypertensive Rats Deprived of Dietary Potassium. R. H. Rosenman, S. C. Freed, and M. K. Smith. *Am. J. Physiol.* 177: 325, 1954.

Unilateral nephrectomized rats were rendered hypertensive by renal figure-of-eight ligature or desoxy-

corticosterone. Their blood pressure was then lowered by dietary potassium restriction. Cortisone acetate restored the elevation in blood pressure even though the potassium deficit persisted.—M. J. OPPENHEIMER

Brain Potassium Exchange in Normal Adult and Immature Rats. R. Katzman and P. H. Leiderman. *Am. J. Physiol.* 175: 263, 1953.

Radio-potassium was administered by intraperitoneal injection to normal adult male rats. They were sacrificed at intervals at which time brain and plasma radioactivity was determined. Influx into brain was 2.89 mEq/Kg./hr., outflux 3.64 mEq/Kg./hr., ratio was 0.80. Since there is a steady state, 20 mEq of K/Kg. of wet brain is not exchangeable with K^{42}. Four- and 15-day rats have an influx of 3.9 mEq/Kg./hr. This value is 3.1 in 35-day rats. In these last three groups all brain potassium is exchangeable. These studies supply some much needed data on electrolytes in the central nervous system.—M. J. OPPENHEIMER

Effect of Adrenalectomy, Desoxycorticosterone and Cortisone on Brain Potassium Exchange. P. H. Leiderman, and R. Katzman. *Am. J. Physiol.* 175: 271, 1953.

Adrenalectomized rats were maintained on saline for 5–7 days. After intraperitoneal injection of radioactive potassium they were sacrificed at various intervals. At this time brain and plasma activity was investigated. Inflow of potassium into brain is not changed by adrenalectomy. These experiments indicate that all brain potassium may be exchanged in adrenalectomized but not in unoperated rats. In normal animals there is a nonexchanging compartment. This last mentioned compartment is restored by cortisone in adrenalectomized rats. Saline and DOCA fail to do so. Potassium inflow into brain is not influenced by plasma levels. The authors suggest that brain potassium system is carrier limited.—M. J. OPPENHEIMER

ITEMS OF GENERAL INTEREST

Some Psychosomatic Aspects of Food Allergy. W. Kaufman. *Psychosom. Med.* 16: 10, 1954.

Patients sometimes experience untoward reactions following ingestion of certain foods. These reactions may be caused by an allergic phenomenon, by psychologic factors, or by a combination of both. Emotional disturbances during eating can readily result in such psychosomatic reactions as nausea, vomiting, epigastric discomfort, intestinal cramps, aerophagia, belching, and diarrhea. Furthermore, an emotional disturbance may accentuate an allergic response. For example, a patient may experience a mild attack of vasomotor rhinitis lasting fifteen minutes after he drinks orange juice for breakfast. However, if the same patient drinks orange juice during a period of repressed resentment, he may develop a more prolonged and intense attack of vasomotor rhinitis.

An allergic reaction to food may cause secondary emotional disturbances. Several case histories are reported in which patients developed emotional symptoms such as mental confusion, forgetfulness, bizarre behavior, and even a paranoid state. These symptoms cleared up completely when the noxious allergen was removed from the diet.

Some patients knowingly will eat foods to which they are allergic because these foods have a special symbolic meaning for them. For example, a certain food may offer a person a feeling of security, or, a certain food may be eaten because it represents a reward, or, at times specific foods may be eaten because of pleasurable association. Then there are patients who will eat allergenic foods because of a conscious or unconscious need to punish themselves. Psychotherapy can help these patients to modify their diets and abstain from allergenic foods.

The management of patients with food allergies requires allergic therapy and psychotherapy. The allergic therapy will uncover the noxious allergen and regulate the diet. Psychotherapy will remove or alleviate the psychogenic factors.—S. W. CONRAD

"Wheat-free" Diet in the Treatment of Sprue. J. M. Ruffin, D. D. Carter, D. H. Johnston, and G. J. Baylin. *New England J. Med.* 250: 281, 1954.

In 1950 it was observed that patients with celiac disease improve when wheat and rye flour are excluded from the diet. Investigation has since incriminated the gluten fraction of rye and wheat as the responsible factor. Ruffin and associates made use of this information in the treatment of a thirty-nine-year-old housewife with prolonged steatorrhea. The patient showed the characteristic clinical and laboratory evidences of sprue. There had been no response to a low fat, high carbohydrate, low protein diet supplemented by vitamins, intramuscular liver extract, folic acid, calcium, and vitamin B_{12}.

The patient was given a "wheat-free" diet with no medication except calcium. Within two weeks there was a noticeable clinical improvement and a decrease in the number of bowel movements. In three months on this diet the patient gained 43 lb, and diarrhea had ceased. X-ray studies showed that the small bowel pattern, which rarely returns to normal during remisson, became normal three months after treatment started. Total protein, albumin-globulin ratio, and serum calcium also reverted to normal levels. An improvement was seen in the vitamin A and glucose tolerance curves. Although this is a single case report, and sprue is notoriously unpredictable in its spontaneous remissions and exacerbations, the rapid and dramatic improvement strongly suggests that remission was induced rather than spontaneous. The

authors emphasize that these are only preliminary observations, though two additional patients with the sprue syndrome were being treated with the wheat-free diet with similar results.

It is interesting that the former dietary regimens prescribed for sprue, such as the banana diet, the vegetable-fruit diet, and the starch-free diet, all had in common the elimination or curtailment of wheat. —M. W. BATES

Basal Metabolism in Nutritional Edema. P. S. Venkatachalam, S. G. Srikantia, and C. Gopalan. *Metabolism* 3: 138, 1954.

In a continuing study on metabolic alterations in subjects suffering from starvation and nutritional edema, the authors report on the basal metabolic rates in the presence of malnutrition and edema. At the height of edema, a subnormal basal metabolic rate was observed. Following treatment, there was an absolute rise in basal metabolism and a fall in body surface area. There was a pronounced rise in BMR per square meter per hour after treatment. The reduced BMR during edema was closely correlated with the reduction of metabolizing tissue and not to any reduction in oxygen consumption per unit of metabolizing tissue.—C. R. SHUMAN

Improved Fertility and Prevention of Abortion after Nutritional-Hormonal Therapy. S. J. Glass and M. L. Lazarus. *J. A. M. A.* 154: 908, 1954.

The authors postulate that many cases of functional infertility and abortion may result from errors in sex hormone metabolism associated with variable degrees of nutritional and hepatic insufficiency. A group of 22 men and 50 women was studied by standard methods in relation to sterility. Sixty-eight per cent of the women were nulliparous and the duration of the infertility in the total group of women varied from 2 to 16 years. Fourteen had impaired or borderline abnormal liver function as determined from liver function tests (BSP, flocculation tests, etc.).

The patients were given an optimal caloric intake, a protein content of 1.5 to 2 Gm. per Kg. of body weight, foods rich in vitamins, and in some instances multivitamin capsules of relatively high potency. After one to two months on this regimen, men were given testosterone propionate 50 mg. every other day by intramuscular route until a total of 500 mg. had been given. The women received oral estrogen and buccal progesterone therapy according to a schedule given in the original article.

Of the 34 nulliparous women receiving nutritional and hormone therapy, 56 per cent achieved pregnancy, as compared with only 16 per cent of 31 nulliparous women receiving hormonal therapy alone. Similarly, improved spermatogenesis occurred in 15 of 17 men receiving nutritional and testosterone therapy, as compared with only 4 of 10 men who also had oligospermia but received gonadotropic therapy alone. According to the authors, these differences are statistically significant.

On this basis, the authors believe that "prolonged saturation with the beneficial food supplements, inherent in the nutritional regimen, renders the entire reproductive system more responsive to endogenous as well as exogenous sex hormones so that gametogenesis progresses to full and efficient maturation."—S. O. WAIFE

Comparison of Anabolic Effects of Testosterone Cyclopentylpropionate with Testosterone Propionate. K. R. Crispell, W. Parson, and R. Gahagan. *Metabolism* 3: 78, 1954.

Two subjects were placed on a standard metabolic regimen and nitrogen excretion baselines were established. They were injected intramuscularly with 300 mg. of testosterone cyclopropionate. After return of nitrogen excretion to the baseline, 300 mg. of the testosterone propionate was given. The period of nitrogen retention was definitely more protracted with the former agent and the total nitrogen retention was also greater. The 17-ketosteroid excretion rates were elevated for about 11 days with the depot form, compared with an average of 5 days with testosterone propionate.—C. R. SHUMAN

Effect of Somatotropic Hormone on Growing Rats on a Diet Deficient in Vitamin B_2 Only. A. R. Colange and A. Raffy. *Compt. rend. Soc. de Biol.* 146: 1909, 1952.

Previous experiments have shown that when young male rats are deprived of vitamin B_2 growth is arrested, the pituitary undergoes alteration, the thymus disappears, and the genital system becomes atrophied. Injection of gonadotropic hormones will, in B_2-deficient animals, stimulate genital development, although growth remains deficient.

In the present investigation, the authors studied the effect of pure somatotropic hormone on young riboflavin-deficient rats.

In the first experiment, a male albino rat on a standard diet was compared with 2 rats on a riboflavin-deficient diet; one rat received 3 times daily an injection of 0.25 cc. of a solution of 5 mg. per cc. of somatotropic hormone. In another study of 3 riboflavin-deficient rats, one was given a daily supplement of 20 μg. of riboflavin, and one received an injection of 1 mg. of somatotropic hormone in 3 divided doses. The animals were weighed 3 times weekly and sacrificed after 23 days. Finally, 5 adult male albino rats were treated according to the same experimental design, except that 2 of them received the riboflavin-deficient diet plus somatotropic hormone. These animals were sacrificed on day 35.

Growth occurred in all 5 rats, but was markedly impaired in the 3 animals on the deficient diet.

Weight increases were: 236 per cent in normal control; 252 per cent in rat on diet deficient in riboflavin but supplemented with the vitamin; and 55 and 25 per cent, respectively, in the 2 rats deprived of riboflavin and receiving somatotropic hormone.

Thus, the somatotropic hormone employed had no effect on weight or length of rats deprived of vitamin B_2. In the rats weighing 25 Gm., growth was arrested, and it was just as clearly slowed in the rats weighing 40 Gm. Internal organs of rats on the riboflavin-deficient regimen revealed practically the same degree of development whether they had received the somatotropic hormone or not. The spleen and genital tract were slightly more developed in animals receiving the hormone injections.

Although somatotropic hormone has been shown to promote growth in hypophysectomized rats, it is obviously ineffective in animals deprived of riboflavin. It would therefore seem that the growth-stimulating effect of somatotropin is dependent in part on vitamin B_2.—C.-J. HOWELL

Methionine—Origin of Sunlight Flavor in Milk. S. Patton and D. V. Josephson. *Science* 118: 211, 1953.

Experimental evidence is presented to demonstrate that the chemical reaction induced by the radiation of methionine in the presence of riboflavin with the light of the visible spectrum is responsible for the objectionable sunlight or activated flavor of milk. This reaction can take place either in distilled water solutions of methionine (20 mg./qt.) upon 1-hour exposure to sunlight, or in skim milk to which *dl*-methionine has been added. Cysteine or cystine did not augment the sunlight flavor in skim milk. Thus, the flavor appears to result rather specifically from photolysis of methionine.—M. K. HORWITT

Nitrogen, Water and Electrolyte Metabolism on Protein and Protein-Free Low-Caloric Diets in Man. 1. Water Restriction. M. Quinn, C. R. Kleeman, D. E. Bass, and A. Henschel. *Metabolism* 3: 49, 1954.

The authors have conducted an extensive study of the influence of water restriction upon numerous metabolic determinants, including body water, electrolytes, nitrogen balance, and body fat in 10 normal subjects receiving both protein and protein-free low calorie diets. Both groups showed negative water balances, with that of the protein group exceeding that of the nonprotein group. The excessive water losses of the protein group were caused by the increased excretion of protein metabolites. Water losses were made up principally from the extracellular compartment. However, dehydration was not a prominent feature in either group. The calculated internal balances indicated large losses of cellular potassium and entry of sodium into cells. Ketonuria occurred in the protein-fed group, possibly through the formation of glutamic acid which may have the ultimate effect of decreasing oxalacetate replenishment through the diversion of ketoglutamate from the Krebs cycle. The reduction of acetate oxidation would then lead to increased acetoacetate formation. Nitrogen balance was not improved by the addition of protein to the diet; it was used rather as a source of energy.—C. R. SHUMAN

Effect of Posterior Pituitary on Water Metabolism in Thiamine Deficiency. K. Guggenheim. *Metabolism* 3: 44, 1954.

Like protein-deficient animals, rats maintained on a thiamine-deficient diet exhibit a delayed diuretic response to a water load. Pitressin was found to exert a more potent and lasting effect in the deficient animals than in control animals. The thiamine-deficient animals were found to excrete larger amounts of pitressin following injection of the hormone than did the control animals. It was shown that the ability of the liver to inactivate pitressin was impaired in thiamine deficiency. It was assumed from these data that the failure to inactivate pitressin may be one of the causes of water retention in both thiamine and protein deficiences.—C. R. SHUMAN

Adrenal Cholesterol, Liver Glycogen and Water Consumption of Fasting and X-Irradiated Rats. L. F. Nims, and E. Sutton. *Am. J. Physiol.* 177: 51, 1954.

Two days of fasting produce changes in water intake and liver glycogen levels in rats. These do not take place after hypophysectomy. It may be suggested that the changes in water intake and liver glycogen are the result of a slowly developing stress. When rats have their whole bodies exposed to x-ray, part of the response is due to a stimulation of the pituitary-adrenal system. However, decreased food intake also plays a role. Increase in water intake and fall in adrenal cholesterol depend on increased stimulation of adrenal by anterior pituitary. The early fall in hepatic glycogen is due to decreased food intake. The magnitude of this decrease in liver glycogen is reduced by pituitary-adrenal activity after irradiation, so that it is less than it would be of caused by fasting alone.—M. J. OPPENHEIMER

Factors Influencing Betaine Aldehyde Oxidase Activity of Rat Livers. F. L. Humoller and H. J. Zimmerman. *Am. J. Physiol.* 177: 279, 1954.

The betaine aldehyde oxidase system is increased in activity by magnesium, aluminum, diphosphopyridine nucleotide, and adenosine triphosphate *in vitro*. This same system is inhibited by betaine, aureomycin, alcohol, and calcium ions. A diet high in fat but low in choline reduces the activity of this enzyme system in rat livers. When this same diet is fortified with vitamin B_{12}, glycine, homocystine, or methionine, betaine aldehyde oxidase and choline oxidase systems activity of the liver increases but not its fat

content. Choline injected simultaneously with betaine aldehyde increases the toxicity of the latter substance. However, choline given one-half to one hour before betaine aldehyde decreases its toxicity. Atropine is without effect on betaine toxicity.—M. J. OPPENHEIMER

The Use of Oral Choline in Cystinuria. V. Coxan and F. O. Kolb. *Metabolism* 3: 255, 1954.

In this study, urinary cystine was determined by converting it to cysteine and using the nitroprusside reaction for the measurement of sulfhydryl groups. It was felt that this technique was satisfactory for the examination of day-to-day changes in cystine output and that the largest output appeared in the patient with the most severe disease. The administration of choline chloride in doses of 3 to 8 Gm. daily was without effect on the cystinuria observed in these patients.—C. R. SHUMAN

Glycogen Fractions of Cardiac Muscle in the Normal and Anoxic Heart. A. W. Merrick and D. K. Meyer. *Am. J. Physiol.* 177: 441, 1954.

When dogs succumbed to anoxia produced by pneumothorax the total cardiac glycogen and trichloracetic acid-soluble glycogen are both reduced, but these latter more so. This indicates that trichloracetic acid-soluble glycogen was converted to residual glycogen. One hour after hearts were excised similar changes in glycogen were noted. However, the soluble portion increased from 2.5 to 7.5 hours after excision. Total glycogen continued to fall during this period. Species differences were marked for these two forms of glycogen. The authors are of the opinion that these data support the idea that these two forms of glycogen are physiological entities. —M. J. OPPENHEIMER

Failure of Cortisone and Hydrocortisone to Replace Pteroylglutamic Acid and Citrovorum Factor in Microbial Growth. J. H. Jandl. *Proc. Soc. Exper. Biol. & Med.* 85: 166, 1954.

Previously it had been reported that dehydroisoandrosterone and cortisone would replace pteroylglutamic acid and citrovorum factor in supporting the growth of certain lactic acid-producing bacteria. In the study here reported, cortisone acetate, cortisone, and hydrocortisone were evaluated under the same conditions. The organisms used were *S. faecalis, L. casei,* or *Le. citrovorum.* Cortisone and hydrocortisone added to standard assay media failed to support or to potentiate the growth of any of these organisms. —L. W. KINSELL

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